FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

8:30 a.m.

Tuesday, October 6, 1998

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Holiday Inn
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Silver Spring, Maryland

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C O N T E N T S

Epivir-HBV (lamivudine tablets and oral solution)
Glaxo Wellcome, Incorporated,
for treatment of chronic hepatitis B

PROCEEDINGS

(8:30 a.m.)

DR. HAMMER: Good morning. I'd like to open today's session of the Antiviral Drugs Advisory Committee meeting.

Today we are happy to welcome Glaxo Wellcome, the sponsor, of lamivudine which we're going to consider for the treatment of chronic hepatitis B, and we will have, I think, a very interesting day discussing this drug and this issue.

I'd like to start by having the members and guests of the committee and members of the agency introduce themselves. I'll start on my right with Dr. Jolson.

DR. JOLSON: Good morning. I'm Heidi Jolson, Director of the Division of Antiviral Drug Products.

DR. STYRT: Barbara Styrt, medical officer, Division of Antiviral Drug Products.

MS. KUKICH: Stanka Kukich, acting medical team leader.

DR. SOON: Greg Soon, statistical reviewer.

DR. MASUR: Henry Masur from the Clinical Center, NIH.

DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital, New York.

DR. DIAZ: Pamela Diaz, Chicago Department of

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MS. STOVER: Rhonda Stover, FDA.

DR. HAMMER: Scott Hammer from the Beth Israel Deaconess Medical Center and Harvard Medical School in Boston.

DR. HAMILTON: John Hamilton, Division of Infectious Diseases at Duke University.

DR. YOGEV: Ram Yogev, Division of Infectious Diseases, Children's Memorial Hospital, Chicago.

DR. SO: Sam So, Stanford University, Director of the Stanford Asian Liver Center.

DR. LEE: Sam Lee, hepatologist from the University of Calgary, Canada.

MS. MELPOLDER: I'm Jackie Melpolder. I'm the patient rep and also work at the Clinical Center at NIH.

DR. FLETCHER: Courtney Fletcher from the Department of Clinical Pharmacology at the University of Minnesota as a consumer rep.

DR. HAMMER: Thank you.

I'd like to turn to Rhonda Stover now who will read the conflict of interest statement.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with the provisions of 18 United States Code 208(b)(3), full waivers have been granted to Dr. Hamilton, Dr. Masur, Dr. Hammer, Dr. El-Sadr, and Dr. Feinberg. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported involvements which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ram Yogev would like to disclose that Glaxo Wellcome is providing funding for a study of amprenavir in pediatric patients.

Dr. Courtney Fletcher is the principal investigator in a Glaxo Wellcome funded study of antiretroviral therapy. Glaxo Wellcome provides Retrovir and lamivudine for the study.

Lastly Dr. Maria Sjogren would like to disclose that she is a co-investigator in a protocol using lamivudine for renal disease in patients with chronic hepatitis B. The study is supported by Department of Defense funds. No pharmaceutical company support is received.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. HAMMER: Thank you.

I'd like to turn now to the Director of the division, Heidi Jolson.

DR. JOLSON: Thank you, Dr. Hammer, and good morning, ladies and gentlemen.

First I'd like to welcome our returning advisory committee members and to also offer our sincere thanks to today's consultants for joining us for this meeting. I know several of them traveled quite a long

distance to be here today.

The division would also like to acknowledge Glaxo Wellcome for their willingness to share their data today. I believe that we in the division well recognize that the design and conduct of clinical trials for hepatitis therapies are particularly challenging. I think that will be evident today. In this regard, the sponsor's efforts in conducting this large development program for their already-marketed product, lamivudine, should be acknowledged.

Additionally, the agency appreciates the participation of the patients in these trials. Their participation has significantly contributed to the understanding of the safety and efficacy of this therapy.

In the next few moments, I'd like to share my perspective on today's meeting.

1998 has been an important year of progress for treatment of chronic hepatitis B and C. Earlier this year in May, this committee met to discuss the first application for a nucleoside analog used in combination with alfa interferon to treat relapse patients with hepatitis C. Rabavirin, in combination with interferon, was approved in June of this year. Today we meet to discuss an application for the approved nucleoside analog lamivudine, the first oral and the first non-interferon therapy for chronic

hepatitis B treatment. Investigation of the safety and efficacy of this class of drugs represents an important step in development of new treatment options for patients living with this serious disease.

Today's meeting is also an opportunity to emphasize many of the challenges ahead in this therapeutic area. As will become evident in today's presentations, drug development for hepatitis is particularly complex and many questions remained unanswered. For example, today will be the first opportunity for this particular committee to discuss the clinical significance of serologic and virologic changes in patients with chronic hepatitis B.

Ironically, it has been almost three years when this committee was asked to address an analogous question when the original NDA for lamivudine for HIV was presented. At that time, change in HIV RNA was a newly available surrogate endpoint in pivotal trials of HIV therapeutics. As HIV treatment and trial designs have evolved dramatically over the past several years, we anticipate that our knowledge about treatment of chronic hepatitis will also evolve in the years ahead.

We hope to make clear from today's presentations that many issues in drug development still need to be addressed to optimize use of current and future therapies for this disease. These issues include the need

for targeting the appropriate patient populations for treatment, establishing the optimal treatment durations, determining the implications of viral resistance, and importantly demonstrating the clinical benefit of drug therapy.

As always, we look forward to and appreciate your guidance on these and other issues that we will be raised today. Thank you.

DR. HAMMER: Thank you very much.

I'd like to call on Dr. Marc Rubin who will introduce the sponsor's presentation.

DR. RUBIN: Thank you. Good morning.

Over the next few minutes, I'm going to give you a very brief overview of the clinical development program for lamivudine for hepatitis B, and then Dr. Nat Brown is going to take a bit longer to review some of the specific components of that program.

This has been a very high priority for us at Glaxo Wellcome because hepatitis B is a very important disease. Worldwide it is one of the top 10 causes of death. The CDC estimates that there are 300 million or so people that are infected with hepatitis B worldwide. 75 percent of those are in Asia, and in fact about half of them are in China specifically. It is estimated that between a quarter and 40 percent of those individuals will

die either of hepatitis or of hepatitis B related complications.

Hepatitis B is also a significant concern in the United States where there are a little over a million individuals infected with the virus, and it is estimated that over the next year, there will be 17,000 hospitalizations in the U.S. and over 5,000 deaths due to hepatitis B.

Interestingly, while we typically think of the disease in Asia as being transmitted in the perinatal period and the disease in the western world as being transmitted horizontally, in fact even in the United States, up to 30 percent of people who have hepatitis B have acquired it in the perinatal period.

Well, somewhat analogous to HIV, hepatitis B is a disease that's driven by viral replication. Accordingly, we believe that the main goal of therapy is to produce sustained reduction in viral load ideally before advanced disease sets in. Although it's difficult to actually show this in short-term clinical trials, I think it's logical to assume and we believe that if we can achieve longer-term reduction in viral load relatively early on, we can perhaps prevent the chronic sequelae of hepatitis B, particularly cirrhosis and hepatocellular carcinoma.

With hepatitis B, there are really two ways to

achieve a reduction or longer-term reduction in viral load. The first is to use an agent that's associated with seroconversion which achieves reduction in viral load, and that of course, happens with interferon. As we will also see, that occurs with lamivudine.

The second, and somewhat analogous to HIV, is to continue potent antiviral therapy to sustain that drop in the viral load.

Interferon alfa now is the only approved therapy. It's given by injection for up to six months. It is, of course, associated with an increase in loss of HBe antigen compared to those that don't receive it. Many patients don't respond to interferon. The histologic benefit is essentially limited to those patients who do achieve long-term drops in viral load, signaled by HBe antigen loss and seroconversion. It's injectable. It does have a certain number of adverse reactions that overall limit access and effectiveness of the therapy.

This is a map that just reviews the locations of the clinical programs that Glaxo Wellcome has undertaken with lamivudine and hepatitis B. It's a global disease obviously, and this has been a truly global program for us. So, we've had ongoing parallel programs, of course, in North America and in Europe, but importantly, a large focus of the program has also been in Asia.

The data that is in the NDA that you have reviewed then comes from patients in trials from all of these countries. We feel it's extensive. There are 21 phase I and phase II trials, enrolling just over 500 patients. There are four principal phase III trials, and Dr. Brown will review the safety and efficacy from those trials that have enrolled just under a thousand patients. In addition, there are about 4,000 patients enrolled in a variety of other controlled and uncontrolled trials and a large compassionate use program as well.

So, the key features of lamivudine, we believe, that are supported by the data are, first, that it does offer the first oral therapy for chronic hepatitis B. You'll see that it reduces hepatic necroinflammatory activity in the majority of patients, and it also retards the progression of fibrosis. We see enhanced HBe antigen seroconversion, better than is seen with placebo and in a similar range to that seen with interferon. We see an increased frequency of ALT normalization and overall a quite favorable safety profile.

We believe that the data will support then our proposed indication for Epivir-HBV for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and with liver inflammation.

And I will turn over the podium to Dr. Brown.

DR. BROWN: Thanks, Marc. It's a pleasure to be here today before the committee and its consultants and agency staff. Nearly four years ago, we met with members of the committee and agency staff to discuss the principal endpoints and designs of hepatitis B trials, and I'm pleased to be able to present the results of the planned studies today from our principal phase III controlled studies and other data as well.

A brief overview of my talk. Two slides on disease-related background, two slides on some of the key features of the preclinical aspects of lamivudine. And as Marc mentioned, today I'll be concentrating especially on the clinical data from the four controlled studies, but we will review the key findings with regard to clinical pharmacology for lamivudine in hepatitis B patients and also briefly review data from other studies.

Hepatitis B virus is a quite small DNA virus, a small genome with overlapping reading frames, four principal genes. The hepatitis B surface antigen gene encodes the envelope glycoprotein. The core antigen gene encodes the capsid proteins comprising nucleocapsid shell within the enveloped Dane particle. The hepatitis B polymerase also has a reverse transcription function, as most people here are aware. Polymerase here is illustrated as attached to a DNA strand within the viral particle.

Inside cells the virus makes an X protein which can function has a transcriptional transactivator, but the role in the viral life cycle is essentially poorly understood.

An important facet of this virus is that the first DNA template is replicated from an RNA transcript, so there's a reverse transcription step which makes the reverse transcriptase activity of the polymerase a potential target for antiviral therapy just as for retroviruses.

Now, the envelope glycoprotein, the surface antigen, is produced in very large quantities in vast molar excess, and it's quite easy to detect in blood. It self-assembles into spherical and filamentous particles, and therefore is used as the primary marker of infection with this virus. It's very easy to detect surface antigen in blood. It's present in such vast excess that it can be detected often in the absence of appreciable levels of viral replication, and as Marc mentioned, the level of virus replication appears to be quite important to the chances for disease progression. So, importantly, we also measure measures of viral replication, serologic measures, such as e antigen, which correlates with high viral replication, and DNA levels as well. In the 1970s and 1980s, polymerase levels were often mentioned, but DNA assays have largely replaced those.

The clinical course of chronic hepatitis B virus infection is quite variable. Chronic infection with the virus is generally defined worldwide as presence of detectable serum surface antigen for 6 months or more in the clinic. This kind of chronic infection has a very broad range of outcomes, but importantly the primary clinical sequelae of this disease and the primary cause of death is liver disease. So, this does differ in some respects from HIV which is obviously a multi-organ disease. So, the whole goal in hepatitis B therapy is to reduce the progressive necroinflammatory disease in the liver which tends to be associated with persistent high levels of virus replication documented usually by either persistent e antigenemia or high levels of DNA or both.

Two slides on the key preclinical facets of lamivudine. As most people here are aware, it's a potent inhibitor of both HIV and hepatitis B virus in vitro at nanomolar concentrations really for both viruses and in various in vitro systems.

Lamivudine is quite potent against hepadnaviruses in several models. The duck system, both in primary hepatocytes and in infected ducks. Quite potent in HBV infected chimps where .3 milligrams per kilogram has produced clearance of detectable virus at conventional hybridization assay levels. Somewhat potent in woodchucks,

partially potent in woodchucks as well.

The lamivudine triphosphate acts as an obligate chain terminator for viral DNA synthesis and is not stably or internally incorporated into cellular or mitochondrial DNA.

Importantly the lamivudine triphosphate molecule has a long intracellular half-life, on the order of 17 to 19 hours, which facilitates once daily dosing.

Most of the toxicologic data was submitted with the original lamivudine NDA application for combination therapy in HIV briefly reviewed here. Preclinical tox studies predicted an overall favorable safety profile. We saw no effects in in vivo mutagenicity and carcinogenicity studies, including long-term carcinogenicity studies. In teratogenicity and reproductive studies, there were no findings except for an increased early fetal resorption rate in rabbits. PK studies in animals essentially predicted good oral absorption and a large volume of distribution.

We've conducted an extensive clinical program in both HIV and hepatitis B patients, including adults and children. Of most relevance today are some dose-ranging studies that we conducted in the patients with chronic hepatitis B in phase II, seven principal phase II dose-ranging studies where we explored doses of 5 to 600

milligrams per day for treatment periods of 1 to 6 months with follow-up added on to that as well. You'll see a little bit of that data in the Q&A.

These are the principal PK results with lamivudine in both hepatitis B and HIV patients. The drug is well absorbed. The time to max concentrations is always under 1 and a half hours. Cmax on the order of 1.1 to 1.5 micrograms per ml, and oral bioavailability around 80 to 85 percent.

There was no food effect on absorption of the drug.

Minimal protein binding. High volume of distribution in people as predicted from the animal studies.

The clinically relevant serum half-life is 5 to 7 hours. The drug is primarily renally cleared as unchanged drug, and therefore no dose modification is needed for patients with hepatic dysfunction. But we do recommend a dose modification with renal insufficiency, and we can go into that detail.

There were no significant differences in the pharmacokinetic behavior of the drug in hepatitis B or HIV patients, nor by gender or ethnic group.

This is the principal observation in phase II with regard to the dose and drug concentration relatedness

of the antiviral effect of lamivudine in hepatitis B patients. On the vertical axis are reductions in HBV DNA, serum HBV DNA, 0 to 100 percent. And on the horizontal axis are the measured drug AUCs from two 1-month dosing studies that were conducted in North America and Europe.

This recounts the doses that were explored, 5 to 600 milligrams per day. So, for doses of 5 to 20 milligrams, illustrated by these data points over here, the antiviral effect was suboptimal, but at dosing levels of 100 milligrams and above, illustrated here by these data points -- and the 100 milligram dose I should mention correlated with daily AUCs over 4,000. At this kind of dosing level, the antiviral effect for lamivudine in hepatitis B patients was indistinguishable both with regard to the percent reduction in HBV DNA, as well as the percent of patients who cleared detectable virus in the solution hybridization assay. So, we call this our equimaximal antiviral effect. So, there's a break point in the dose effect at daily doses of 100 milligrams.

So, the principal phase II observations for hepatitis B patients were that the maximum antiviral effect correlates with doses of 100 milligrams per day or greater. This kind of observation from the early studies was borne out in some later phase II studies and also in one phase III study, the Asian multi-center trial which you'll see.

The 100 milligram dose proved to be superior for sustained HBV DNA suppression compared to the 25 milligram dose that was investigated in that phase III trial.

Throughout these investigations we found no treatment-limiting or dose-related adverse events in these kinds of dosing studies.

As Dr. Rubin mentioned, principally today my goal will be to review the data from the four large controlled phase III studies. Three of these studies were conducted in treatment-naive patients, one in interferon nonresponders with the thought that this group could be biologically distinct. Three of these studies were placebo-controlled and that included a U.S. multi-center trial, as well as an Asian multi-center trial, in treatment-naive patients. The study in interferon nonresponders was an international study that was also placebo-controlled. We conducted one what we called active control design which compared lamivudine to interferon monotherapy to the combination, and conducted that in treatment-naive patients in Europe, Canada, and a number of countries around the world.

This first slide illustrates the study designs for the two placebo-controlled studies in treatment-naive patients. This was the study that was published in the New England Journal in July, a multi-center study in Southeast

Asia, 358 patients overall, randomized 2 to 2 to 1 to lamivudine 25 milligrams per day or 100 milligrams per day or placebo.

The commonalities of phase III included a primary treatment period of 52 weeks or 1 year, if you will. Those are illustrated on this slide and the next. So, patients were treated for 1 year and the primary treatment comparisons were at week 52 for histology as well as for serologic endpoints. In this study there was no follow-on period per se. Patients were offered enrollment directly into a follow-on study called 3018 which you see a little bit of data from.

The primary goal of this trial was to measure improvements in liver histology. Liver biopsies were done pretreatment at baseline and at 1 year.

This study actually was about 90 percent treatment-naive. There were 10 percent of patients that had some previous exposure to interferon. The other trials were, in a sense, 100 percent treatment-naive.

The U.S. multi-center trial has been reported at a meeting this spring. This study was also a 1-year comparison, a straight ahead 1-to-1 randomization of lamivudine 100 milligrams per day compared to placebo. Treatment comparisons at week 52. A controlled off-treatment follow-up period to provide controlled safety

assessments post treatment, 16 weeks long, and then the study participation ends at week 68. 141 patients on that U.S. trial.

This is what I mentioned as the active control design study, lamivudine monotherapy for a year, 100 milligrams per day. This is the interferon monotherapy arm, and I should mention that in this trial all patients were blinded during the first 8 weeks of treatment. At week 8, the investigators opened an envelope to determine whether the patient was assigned to an interferon treatment. There is no true placebo for interferon, as we know, so at this point these two arms remain blinded to each other, but the lamivudine patients continue on monotherapy. So, interferon starts here on this kind of design.

This design of this kind of treatment regimen is essentially identical to the design that was used in the U.S. multi-center registration trial for interferon. A standard course of interferon was given here for the standard 16-week regimen. Then just as in the U.S. multi-center trial, primary treatment comparisons were 6 months post-treatment for both histologic change and for serologic markers. So, this is the nature of the data, the registration studies for interferon. So, again, that fit nicely with treatment comparisons at 1 year.

This is the exploratory combination arm in this kind of study. Patients in this arm would have been taking active lamivudine during the first 8 weeks as well as during the interferon period, and again follow-up with primary assessments at week 52.

The goal of this kind of design, this kind of combination arm, was to explore whether pre-reduction in viral load would offer an enhanced seroconverting effect afforded by interferon and lamivudine during this period.

The interferon nonresponder trial, lamivudine 100 milligrams for 1 year, placebo-controlled for 1 year, and then the same kind of exploratory combination arm with primary treatment assessments at week 52.

This study had a unique feature that the lamivudine patients who were half the patients overall, a 2 to 1 to 1 randomization. Lamivudine patients were secondarily randomized 1 to 1 at this point to either continue with active lamivudine or silently switch to placebo. This was a way to get some control data, exploratory data, for treatment beyond week 52.

The patient population is pretty standard for those who work in the hep B arena, chronic hepatitis B, surface antigenemia, e positive or DNA positive by conventional hybridization, persistently elevated ALTs or evidence of chronic inflammation on baseline liver biopsy,

and no signs of hepatic decompensation. This allowed us to get control data.

The two principal phase III efficacy endpoints. Our goal was to, number one, try to look at improvements in liver disease that might be afforded by therapy. Our primary analysis of reduction in the necroinflammatory liver disease was a 2-point or greater decrease in total Knodell Histologic Activity Index. So, that was really the primary analysis of reductions in liver inflammation, if you will.

We also felt that it would be important to assess changes in liver fibrosis, so we did that as well, and you'll see some of that data using a so-called ranked assessment technique.

The e loss and e conversion analyses are delineated here. E loss, of course, is reduction of e antigen to below detectable. In most of the interferon trials, the primary endpoint was either e loss alone or e loss combined with DNA loss, and again typically measured 6 months post treatment in those studies.

The e conversion. In our program, we featured the analysis of what we call full seroconversion which is loss of e, gain of antibody to e, and simultaneously undetectable DNA in the hybridization assay. So, this was the protocol featured analysis of e conversion.

We had another definition because we also wanted to be able to refer back to historical data from the 1980s or so when DNA assays were not conventionally used. We looked at an alternate definition of loss of detectable e and gain of antibody, and we looked at sustained e conversion.

So, those were the two most important efficacy endpoints in the program.

We looked at other parameters as well. ALT response and sustained ALT response delineated here, sustained to either end of treatment or to study end. ALT levels over time, just as one looks at those in the individual patient in the clinic. DNA response data and DNA levels over time. S antigen loss, of course, in a sense an ultimate marker of loss of infection, and then safety comparisons, both clinical adverse events and laboratory abnormalities.

Right into the baseline demographic data, quite typical of adult chronic hepatitis B populations around the world, patients typically ranged from their mid-20s into their 50s. Mean age is illustrated here in the mid-30s.

The gender prevalence of the disease in the population tends to be on the order of 70 to 80 percent male and 20 to 30 percent female. In fact, that's the ratio that we enrolled in our trial program. There is an

interesting biologic observation in the literature that chronically infected females from childhood appear to have a higher rate of spontaneous resolution of this disease, and the disease in females may be milder in adults.

The two most prevalent ethnic groups in our studies were caucasians and Asians, as illustrated here, but other groups were included as well in the worldwide program.

In each trial in the case record form, we asked for recognized possible routes of acquisition of this infection typically recounted by the patient to the physician. The three most important categories -- overall the most important category was unknown. Most patients didn't seem to know how they got their HBV infection, and that may actually reflect worldwide reality. Now, in the West, the second most common category was history of sexual contact with a known infected individual. This was a relatively uncommonly recognized route of acquisition in the multi-center Asian study. In the Asian study, the most common category, other than unknown, was known vertical or perinatal acquisition, if you will, whereas this category finished in third place in the three western studies.

The baseline disease characteristics, again quite typical of an adult chronic hepatitis B population and similar in many respects to the interferon trials.

Baseline histologic activity index on the order of 7 to 10 in most of the studies except for the European/Canadian active control study where the baseline score was somewhat lower, possibly due to pathologist variation.

The percent of patients with cirrhosis in the treatment-naive studies was pretty typical, 5 to 10 percent. The interferon nonresponders did have a higher proportion of patients who had histologic cirrhosis at baseline.

DNA levels across phase III averaged around 100 picograms, quite similar to the interferon studies.

In the three western studies, baseline ALT levels were typically around 2 and a half to 3 times the upper limit of normal, as had also been previously observed in interferon studies.

In the Asian multi-center trial, this is the only study where we allowed patients with normal ALTs to come on study by protocol, and they comprised about a third of the patient population overall. So, the median ALT in that study was lower.

So, right into the results, if we could. These are the results of the treatment comparisons on the primary endpoint of a 2-point or greater decrease in Knodell HAI, which we defined as histologic response. In the three placebo-controlled studies, the Asian multi-center study,

the U.S. multi-center study, and the international interferon nonresponder study, in all three, this was the primary treatment endpoint. We see a very consistent treatment effect with regard to lamivudine patients achieving a histologic response significantly more often than placebo treated patients in yellow here. This compares and was always highly statistically significant.

Here's the overall phase III result for histologic response, now including the European/Canadian study of interferon nonresponders and including the combination therapy arm from -- I'm sorry -- the European/Canadian study in treatment-naive patients and the international study with interferon nonresponders had a combination therapy arm.

You've seen this data on the previous slide. Here's the lamivudine versus placebo comparisons from the three placebo-controlled studies. This now includes the histologic comparisons to interferon monotherapy as well as combination.

One important message from our program is that in these kinds of combination designs, at least, we did not really see any real advantage for that kind of combination therapy regimen histologically or serologically, as you'll see.

Interferon monotherapy. The overall result for

treatment arms containing interferon tended to be in the overall program intermediate between lamivudine and placebo but within the European/Canadian study, lamivudine had a slightly higher percent but was not distinguishable from interferon in that particular analysis. The overall lowest response rates were in the combination arm.

Now, this is the analysis of the other important histologic endpoint that I mentioned earlier, the worsening of fibrosis over the course of a year of study. We felt this was important insofar as it may be a link to long-term benefit. It may connect with an ability to retard the progression to cirrhosis. We also felt it might be difficult to show improvements in scarring of the liver, but at least an effective antiviral might be able to retard progression of hepatic fibrosis.

Here we see the result of the two treatment-naive studies in which the lamivudine treated patients, again in red, experienced a progression of fibrosis significantly less often compared to the placebo patients in yellow. Both of these comparisons were highly significant.

In the interferon nonresponder study, we did not achieve significance for this kind of treatment difference which was in the same direction, but overall patients had a lower progression in their fibrosis possibly

because they already had advanced disease at the time at baseline.

Some of the principal serological endpoints are illustrated in the next few slides. HBe antigen loss generally precedes or is sometimes simultaneous with the detectability of antibody to e, but we display the e loss results first because often biologically this is the first thing that's observed in the clinic. This was also the principal endpoint used in most of the interferon studies earlier in this decade.

So, in the western trials, we consistently saw e antigen loss rates at 1 year above 30 percent. Somewhat ironically, for a reason you'll see in a moment, the highest e antigen loss rate was actually in the interferon nonresponders, 33 percent in the lamivudine group versus 13 percent in placebo in that study. These comparisons were not statistically compared because, as I mentioned, we featured the analysis of what we called full seroconversion for statistical analyses.

Importantly in the European/Canadian study, the e antigen loss rate at 1 year for lamivudine in red and interferon in teal was identical, 22 percent in both treatment groups. There was a somewhat higher rate in the combination arm, but as you'll see on the next slide, seroconversion, while being somewhat higher on the

combination arm in that European/Canadian study, was not actually statistically significant in the primary intent-to-treat analysis. So, for full seroconversion, what we saw again was that full seroconversion in treatment-naive patients, both in the Asian study and the U.S. study, was significantly better on lamivudine.

For the interferon nonresponder study, we had a paradox. I showed you the 33 percent e loss rate at a year, 13 percent in placebo. It appears that perhaps in interferon nonresponders, the development of the antibody to e is somewhat delayed for reasons that are unknown at this point. Full seroconversion and e loss were the same in the placebo group in this study, 13 percent, whereas in the lamivudine arm, 33 percent of patients lost e at a year and only 18 percent had gained had gained anti-e to fill this kind of response definition. The lowest rate of serologic response was in fact in the combination arm. Again, the seroconversion rate for lamivudine monotherapy and interferon was statistically indistinguishable at 1 year.

Here's kind of a clinician-friendly slide. This is ALT levels over time in the patient cohort in the three placebo-controlled studies, placebo in yellow, lamivudine in red. As we saw in the last phase II study, patients treated with lamivudine for 6 months or more

tended to normalize their ALTs, and so the dotted line here indicates the upper limit of normal of ALT.

Incorporating our ALT response definitions, probably the most important one was sustained ALT normalization in which patients had to achieve two normal ALTs and had to maintain that response to the end of the primary treatment period. That kind of observation occurred in 40 to 72 percent of lamivudine treated patients versus 7 to 24 percent of placebo. Those comparisons were always highly significant.

The comparison of sustained ALT normalization for lamivudine compared to interferon in that European/Canadian multi-center study was in fact statistically significant favoring lamivudine monotherapy. So, lamivudine produced sustained ALT normalization in that study in 40 percent of patients compared to 17 percent of the interferon monotherapy patients.

We think that these kinds of effects on traditional, if you will, clinical laboratory markers of disease are due to the kind of marked antiviral effect that we saw in phase II and this simply illustrates the phase III antiviral effect for lamivudine in the three placebo-controlled studies. For lamivudine treated patients, their first visit in the phase III protocols is week 2, and you can see marked drops by week 2.

I need to point out that for the purposes of this kind of display, we actually arbitrarily assigned a value of .8 picograms to undetectable DNA values. We have two types of PCR related data that suggest that the average antiviral effect of lamivudine is actually more like 3 to 4 logs. So, this kind of display is somewhat artifactual in that negative, undetectable values were assigned a value of .8, half the threshold of detectability, so obviously a very marked difference in DNA reductions in placebo versus lamivudine over the course of a year.

So, the summary of our efficacy observations is we saw consistent reductions in hepatic necroinflammatory activity in both Asian and western patients, significant reduction in the progression of fibrosis in the treatment-naive patients, enhancement in e loss and e conversion in treatment-naive patients. We saw e loss and e seroconversion rates at 1 year that are similar to interferon, essentially identical to interferon. There is some confusion in the literature there because again the interferon studies tended to analyze e loss and we've tended to feature the full e conversion definition. And as you saw, we saw significant enhancement of ALT normalization.

Into the safety observations. First we'll see the comparisons of lamivudine to placebo and then

lamivudine to interferon. These are the composite observations for clinical adverse events, lamivudine versus placebo, events in decreasing order of frequency as observed in the trials. As you see, line by line as one goes down to compare lamivudine versus placebo, there really aren't any appreciable distinctions for clinical adverse events between lamivudine and placebo in chronic hepatitis B patients over a year.

This just continues that list at lower frequency levels down to the 5 percent event level, but the observations continued down throughout.

The comparison for lamivudine to interferon is primarily available as a direct head-to-head comparison within the European/Canadian study, the so-called B3010 study. Here again are the clinical adverse events in decreasing order of frequency.

Now, the clinical adverse events were, as you might expect, overall more common on the interferon arm. I want to highlight just a few here for clinical consideration.

Some of these events such as fever and chills, malaise and fatigue, headache, myalgias are known components of the flu-like effects of interferon and most patients can be treated through those kinds of effects. The GI side effects are occasionally included in the flu-

like effects of interferon by some authors.

However, there are other kinds of adverse effects that one sees with interferon that aren't necessarily part of the flu-like syndrome and tend to be a little more persistent and problematic in patients: hair loss and alopecia. There were some CNS effects that we observed in these patients. Dizziness, depressive disorders, and then as you'll see on the next slide, vertigo were all more common in the interferon treated patients. Some other aspects of interferon. Again these are generally well described in interferon labels. Leukopenia, if you will, was significantly more common in interferon versus placebo patients. Anorexia and weight loss were more common with interferon. Joint aches and pains more common and thrombocytopenia as well. So, clinical adverse events -- it appeared that interferon was less well tolerated.

Interestingly enough, in the composite data of clinical laboratory abnormalities during the primary treatment periods, the rate of grade 3/4 ALT elevations was identical in lamivudine treated patients and placebo treated patients illustrated here. There was also no appreciable difference in the occurrence of amylase and lipase elevations relating to the old issue of pancreatitis, if you will. So, the two drugs looked quite

similar. There may be a somewhat higher frequency of CPK elevations, but as we can see on a slide, that didn't seem to have any real substantial impact clinically.

We did special analyses of the issue of post-treatment ALT elevations because these have been observed with vidarabine in the 1980s. They have also been observed with interferon. So, we incorporated kind of a four-tiered analysis of during-treatment and post-treatment ALT elevations. The mildest form of elevation will be just a twofold times baseline for an individual patient. Three times baseline, a little more common, and this tends to correspond to a so-called grade 3 abnormality.

Then the more clinically interesting one tends to be when the patient gets to ALT levels over 500, at which time one might schedule an extra clinical visit or start to get a little concerned. Especially important, of course, are ALT elevations associated with signs of hepatic insufficiency such as bilirubin elevations or clinically serious adverse events.

What we observed when we combined the data from those controlled follow-up periods, I should say what we observed during treatment was no difference between lamivudine and placebo for these kinds of phenomena. But post-treatment we did see a difference and that's illustrated here, a mild overall difference between

lamivudine and placebo for the total event observation rate. The difference tended to be in the kind of mild to moderate, generally asymptomatic for post-treatment ALT elevations, roughly twofold more common with lamivudine compared to placebo, a little more than twofold.

But importantly, there was no difference in clinically severe events post-treatment between patients coming off lamivudine and patients coming off placebo. Those were analyzed in two ways. One was ALT elevations associated with bilirubin elevations, in which case 2 percent of placebo patients and 1 percent of lamivudine patients exhibited this kind of phenomenon in the post-treatment period. No difference there.

And also for clinical serious adverse events, 2 of 200 placebo patients and 5 of 416 lamivudine patients, about a 1 percent post-treatment event rate there for clinically severe adverse events.

Importantly, in the phase III studies, no patients developed clinical liver failure.

With regard to the overall summary of SAEs, deaths, and withdrawals, serious adverse events about the same rate in lamivudine and placebo, 10 and 11 percent respectively. The most common abnormality reported as an SAE was abnormal liver function tests, generally elevated ALTs.

There were no deaths in the primary phase III controlled studies. We did see some deaths in transplant patients in some of the other studies which can be discussed otherwise. Those were generally of the types expected in those patient populations.

Withdrawals were actually a little more common in placebo patients than lamivudine patients in the phase III program, I think emphasizing the underlying severity of the disease. This proportion of patients, 2 and 3 percent respectively, withdrew for adverse events. Other withdrawals were for miscellaneous reasons.

So, the summary of the safety observations essentially is that the clinical adverse events and laboratory abnormalities were similar to placebo during treatment. There was a modest increase in generally asymptomatic post-treatment ALT elevations, but no increase in clinically severe events.

Now, the important issue of antiviral resistance, which of course is relevant to any antimicrobial. With lamivudine, we in a sense had an advantage on this issue because we knew prior to the development program that the YMDD motif, a four amino acid sequence, is conserved between the HIV reverse transcriptase and the hepatitis B reverse transcriptase, and it was known in HIV that this might be a site of

resistance essentially to mutation. So, we prospectively incorporated into the phase III program some comprehensive analyses of the phenomenology of detectable YMDD variants.

The way we did that was to take all available patients at week 52 and at week 104, at the end of 1 and 2 years of study. For patients who had detectable YMDD variants, we then tracked back on their previous sera to determine when the YMDD variant developed. We used PCR methods to amplify DNA and then do a restriction fragment length polymorphism assay to detect the variants.

The overall result of this was that YMDD-variant HBV were detectable at 1 year in the overall studies in 16 to 32 percent of patients at 1 year; 24 percent overall phase III average.

Now, in the limited year 2 data we have, the multi-center Asian cohort has been carried to 2 years now. We saw a 38 percent incidence of detectable YMDD variants in those patients after 2 years compared to 16 percent in the 1-year study group.

Importantly, however, the clinical phenomenology associated with this -- it appears that there is not necessarily a complete loss of clinical response. what we see in patients is that patients with the YMDD variants tend to maintain lower viremia levels, lower HBV DNA and ALT levels compared to their pretreatment values.

They were also significantly better than placebo in several comparisons. The sustained HBV DNA response, for example, was not as good as the patients who retained wild-type, but it was significantly better than placebo after adjustment for baseline covariates.

We saw significantly improved liver histology in the patients with the variants, compared to placebo patients at 1 year, and improved ALT normalization.

So, they retained many of the elements of clinical response.

The one thing that appeared to be perhaps lost was e conversion did not appear in the overall analysis to be significantly greater than placebo. However, patients with the variants do seroconvert, and we're still looking at that issue. Interestingly enough, in the Asian cohort at 2 years with the longest carried-forth cohort, the seroconversion rate in the patients with the variants is 27 percent cumulatively after 2 years.

There were no safety issues identified with the variants. Patients who developed the variants had a low higher incidence of on-treatment ALT elevations but lower incidence at post-treatment, and overall the safety comparisons were not different for any adverse events.

This is important data in the program on the next two slides. This is the Asian multi-center trial.

The first year of treatment is the 3009 study published in the New England Journal to this point. This is the same patient cohort. 90 percent of the patients were carried into a follow-on study called 3018.

This shows the lamivudine treated patients over 2 years divided into two kinds of patients, patients who kept the wild-type illustrated by the solid dotted lines for ALT levels and DNA, and that was the majority of patients. Patients who developed the variants are illustrated by the hatched lines for ALT and DNA.

With regard to virologic response over 2 years, both groups obviously did well in the first year. Patients start to develop the variants in the second half of the first year. After 2 years, the subgroup with the variants was still finishing 80 to 90 percent reduced in their DNA levels compared to their own pretreatment.

This is the corresponding ALT phenomenology. Patients who developed the variants tend to have higher ALT levels pretreatment compared to those who retain wild-type, but as you see here, even the total cohort with the variants at 2 years, the median ALT was 0.9 times the upper limit of normal, in other words, within the normal range. This was 0.7 times normal. So, both finished with normal ALTs at 2 years for the overall cohort.

This is possibly an even more important

analysis. With that kind of previous analysis, that includes patients who develop variants in the second year. Here we've taken the same database but analyzed the data, limited the analyses to patients who develop the variants in the first year, so that we could then follow that kind of cohort forward for another year, so we'd get a full year of additional observation on a cohort who had the YMDD variants. So, again, this is the first year data, very similar to what you saw before.

This patient population is patients who had detectable YMDD variants at week 52 and week 104. What you see for viral load is again patients developing the variants in the second half of the first year.

This is the subgroup who developed the variants by week 52. We see their viral load levels go up a bit. They don't get back to their baseline level, and then it seems to actually level off or even start to trend downward during the second year just by continuing lamivudine treatment.

The patients who maintained wild-type are illustrated here, and again these patients, with undetectable levels, are all assigned a .8 picogram value.

So, there was this kind of what we often call the blip phenomenon with regard to viremia. The viral load often comes up a bit but then seems to stabilize, and in

many patients it actually goes down. We can see this in individual patients.

The associated ALT phenomenology is, of course, in patients with wild-type, again they tended to have lower ALT levels pretreatment. They come down and normalize nicely.

Patients who developed the variants in the first are illustrated here. They come down initially with good ALT response. As they develop the variant subspecies, they start to get an ALT elevation, but again echoing the viremia, the ALT levels seem to stabilize and drop off in year 2.

There are some important preclinical evidence that these YMDD variants may be less replication competent, and some of that has been published now. The variants appear to replicate to lower levels in tissue culture, reported by several different laboratories. Also, work on the variant polymerases, when the methionine is changed to either valine or isoleucine, the methionine at position 552, these are the two mutation patterns we see.

People have worked with those polymerases either cloned or extracted from variants, and it appears that these polymerases not only have reduced affinities for lamivudine triphosphate but also for natural nucleotide substrates. That may explain why the replication overall

is lower with the variants.

The clinical evidence for less replication is what I just showed you to some extent. Patients tend to maintain HBV viremia compared to their pretreatment values when they had wild-type. We have a couple of dozen patients overall who have been discontinued when they developed YMDD variants. What we find there is consistently the virus that returns and becomes the predominant species over time is the wild-type, illustrating that in the absence of the selective lamivudine treatment, the wild-type seems to have a replication advantage.

We think we understand this. This is a molecular model. Again, this should be considered speculative, but this is a molecular model of the HBV polymerase. This is the nucleotide binding pocket within the HBV polymerase. This is where nucleotide triphosphates bind for the enzyme function.

The important mutations are at the 552 methionine locus, and for the methionine to valine, we often see the upstream isoleucine -- leucine to methionine switch. Well, these two points are very close to the nucleotide binding pocket, and we think what may be happening is that the shape of this binding pocket in the enzyme actually changes a little bit, resulting in

decreased affinities for lamivudine triphosphate and other nucleotide triphosphates.

So, the phase III data regarding YMDD variants -- we mentioned the overall incidence. We showed you the data that patients with variants tend to maintain lower viremia and retain at least partial virologic response overall, typically 80 to 90 percent reduced at 1 or 2 years compared to their own pretreatment levels. And patients with the variants retained significant elements of clinical response as we showed. And the in vitro data for reduced replication competence.

Briefly reviewing the other studies, we have four open-label treatment transplant studies. It's very difficult to do placebo-controlled studies in patients with life-threatening disease.

In these studies, we thought we saw promising antiviral effects, reductions in HBV DNA, as you might expect, and in patients with elevated ALT levels at baseline, there appeared to be an ALT normalizing effect. Bilirubin levels improved in the subgroups but had hyperbilirubinemia pretreatment, and albumin levels appeared to improve in some groups as well.

Importantly, we did see more adverse events and serious adverse events in these patient populations. It appeared they were generally of types expected with liver

failure, surgical complications or immunosuppression. We didn't see any new pattern of adverse events that we could pick out.

Some important follow-on studies are currently ongoing. One is actually wrapped, a phase IIb study where explored treatment past a year in an open label fashion. With treatment up to a year and a half, we saw e antigen loss in 10 or 24 patients, 42 percent.

The current phase IIIb, if you will, or III follow-on studies include some follow-on treatment studies for Asian patient cohort and for the North American/European patient cohorts. These are open-label treatment with lamivudine for up to 5 years.

The interim analyses submitted with the NDA indicated we do appear to be seeing some increment in e loss and seroconversion in year 2 for both Asian and western patients.

There's an observational follow-on study for patients who achieved e conversion during phase III. The question is how durable is that when patients are taken off treatment. That's called our 3016 study, and the results of that look quite promising. Patients are coming on to this study with an average of 4 to 6 months median follow-up, 6 months for the lamivudine treated ones. The e has remained negative post-treatment for a median of 6 months

in 94 percent of patients.

We haven't really seen any different safety observations with these longer-term follow-on studies.

We did a pediatric dosing study in Europe and Canada. 53 children and adolescents received one of five doses. We did see rapid DNA reductions in these patients as we expected. These were children with chronic hepatitis B with active disease, rapid HBV DNA reductions. Here we used the Chiron branched DNA assay.

It appeared in this study that a dose of 3 milligrams per kilogram per day produced similar exposures to the exposures in adults at which the equimaximal antiviral effect was achieved. And we saw in kids as well that at that dosing level -- above that dosing level, I should say, the antiviral effects appeared comparable.

We saw no treatment-limiting or dose-related adverse events in the pediatric dose-ranging study.

So, I think as Dr. Rubin alluded to, we expect two kinds of long-term benefit with lamivudine. There's a proportion of patients who will lose e or seroconvert, if you will. That proportion appears to be essentially identical to what you achieve with a full course of interferon therapy at 1 year. We also feel we have an increment in response at 2 years. But in any case, we do see that kind of patient population and the literature

would suggest there is some long-term association with improved clinical outcomes with those kinds of patients.

As Marc mentioned as well, we have plenty of data to show that in patients who don't happen to seroconvert, we do see histologic improvement in liver disease and improvement in ALTs and other clinical benefits.

Our conclusions then are that we've got substantial clinical data derived from nearly 40 studies, to which I think Dr. Jolson might have been alluding, where we see consistent efficacy and excellent tolerability for lamivudine in Asian and western patients, reduced liver inflammation, reduced progression of fibrosis, enhanced e loss and e conversion, and ALT normalization. We think these effects are due to prolonged suppression of virus replication, including partial suppression in the patients who develop the variants.

The safety profile of lamivudine appears comparable to placebo during treatment. There is a modest increase in post-treatment ALT elevations, generally in the grade 3 variety, and generally asymptomatic. No difference in clinically severe events post-treatment compared to placebo.

The data support the idea that lamivudine monotherapy will in fact benefit many hepatitis B patients

worldwide, and we feel is a major therapeutic advance based on its oral bioavailability, as well as its consistent efficacy and safety. The data from that follow-on study, as well as the e antigen data in the program in the study, support the notion that one could consider treatment discontinuation after e conversion in immunocompetent patients. Patients who are immuno-debilitated or on immunosuppressant drugs are known to have a significant risk for reactivating disease, so we do not recommend it in those kinds of patient populations.

I appreciate it.

DR. HAMMER: Thank you very much.

We have time for targeted questions, perhaps 30 minutes or so. I'm going to go around the table. I'd like to ask the committee members to prioritize their questions and ask perhaps their most pressing first two or three questions in deference to other members of the committee who likely have similar questions. I will start on the -- did you have something else to present?

DR. COCCHETTO: Sorry, Dr. Hammer. David Cocchetto. Dr. Goodman was prepared to make some comments on histopathology in this patient population as well.

DR. HAMMER: I apologize.

DR. BROWN: That was my confusion on the agenda, but Dr. Zak Goodman from AFIP would like to briefly

present some of the histologic observations from the program.

DR. GOODMAN: My name is Zachary Goodman, and I am the pathologist who evaluated the liver biopsies from the 3010 and 3011 studies. I was asked by the sponsor to present some of the data and talk about scoring of biopsies.

There are many ways that you can approach evaluation of liver biopsies in a study such as this. I've got them listed on the slide here. The old-fashioned way is the conventional diagnoses of chronic persistent and chronic active hepatitis. That's not adequate, but there are many other ways that have been devised. I'll tell you, just summarize. I've tried all of these and they all work pretty much to the same degree. The one that has been used the most, though, is one which is one of the older ways which is the Knodell score, which is what was used for this study.

Now, the Knodell score really should be called the Knodell-Ishak score because my colleague Kamal Ishak is the pathologist who devised this way of evaluating liver biopsies. This was a scoring method that Drs. Knodell and Ishak came up with in planning a study similar to this type of treatment trial in the 1970s. The study itself was never funded, but they published their method for

evaluating the biopsies.

This was designed so that they could take a large number of biopsies from many patients and come up with some sort of numerical score that could then be used in statistical studies. It wouldn't be used in evaluating a liver biopsy from an individual patient.

What they did was they realized that you could dissect out the different components of injury that one sees histologically. There's the periportal injury. The old term is "piecemeal necrosis," and you could evaluate the degree of that feature and then give that a numerical score and add in extra points if there's severe injury with bridging necrosis. You can do the same for the parenchymal injury or the lobular injury, the portal inflammation, and the same for the fibrosis. Each of these gets a numerical score and then you add them up, and that's what gives you the histologic activity index.

Of course, once you've gotten this data, you don't really have to add them in any particular way. You can evaluate each one separately. You can take out the fibrosis and look at that separately and so forth. But it is a way to approach a large number of biopsies in a fairly uniform fashion.

So, what I'm going to talk about is how we go about doing that and then show some examples from the

placebo-controlled U.S. trial. Just to refresh your memories, those of you who are a ways out of medical school, this is what a normal liver looks like histologically under the microscope. There are portal areas and each portal area has a portal vein branch, an hepatic artery branch, and a branch of the bile duct. The blood comes in through the small portal tracts and percolates through the sinusoids of the liver, bathing the hepatocytes with blood that's both from the portal venus system and from the systemic circulation where the business of the liver takes place. Eventually the blood reaches the central veins and then exists into the systemic circulation.

This is a high power of a normal, very small portal area. This is just to show each portal area has a portal vein branch, an hepatic artery branch, and a small bile duct. There's a little bit of fiber supporting stroma that varies with the size of the portal area. This one is very small, so it doesn't have very much. You notice there are no inflammatory cells here.

Here's a liver biopsy from one of the patients in the study. When there is chronic hepatitis, there are a lot of chronic inflammatory cells that accumulate in the portal area. Here's the portal vascular structures pushed over to the side. The entire portal area is expanded by

chronic inflammatory cells, lymphocytes. Now that we have surface marker studies, we know that most of the inflammatory cells in the center of the portal area are B cells. They sit there and they do their function I suppose of making immunoglobulins, and they tend to stay there after a lot of the other injury dies down. That's probably the least important component of the score.

What's more important is the injury that takes place out at the periphery, at the interface between the parenchyma and the portal connective tissue where T cells are found. The T cells come in contact with the liver cells and cause them to die. That's through a process which goes by several names. The current popular name is interface hepatitis, but the older name is piecemeal necrosis, which was defined as the destruction of liver cells at this interface between parenchyma and connective tissue.

Here is it as high power from one of our patients, and you can see the lymphocytes are coming in contact here with the liver cells. They push their way into the liver cells. They lay down adhesion molecules. They express cytokines, and the lymphocytes -- these are T cells -- send a signal to the liver cells that you are irreversibly infected with the virus and now it's time to undergo apoptosis, activate your suicide genes and die.

And that's what happens. The liver cells die and they're replaced by the expanding portal area.

So, that's something that we can grade. If it's hard to find them, you can search around and find a little focus where there's interface hepatitis B, that would be considered mild.

According to Knodell and Ishak's definition if most of the portal areas have some interface hepatitis, but it's less than 50 percent of the way around the majority, then that would be considered moderate. So, here we have a portal area where there's no interface hepatitis on this side, but there is on this side. So, that would be moderate.

And if it's more than 50 percent of the way around most of the portal areas, then that's considered marked.

Now, I can take a good size liver biopsy and I'll find examples of mild, moderate, and marked in some of the portal areas in each biopsy. So, you have to do a mental average of the overall degree of injury to come up with the score. That's one of the sources of variation in scoring, but it's not too bad.

So, we grade them as mild, moderate, and marked and then look back at the score sheet and assign a number that goes along with these. Mild, according to the

original definition gets a score of 1. Moderate gets a score of 3, and marked gets a score of 4.

Then we can add in extra points if there's severe injury with bridging necrosis. That only happens rarely in viral hepatitis. It's more frequent in autoimmune hepatitis. In the original definition, if you had a moderate degree of piecemeal necrosis plus bridging, you get a score of 5. I've never seen an example of that.

You do occasionally, in viral hepatitis, see a marked degree of piecemeal necrosis with portal to portal bridging or portal to central bridging and that gets a score of 6.

On very rare occasions in viral hepatitis there will be such severe injury that large portions of the parenchyma are destroyed, there's multilobular necrosis, and that would get a score of 10. But a patient with that much injury would be too sick to be in one of these studies. I have very rarely seen this in chronic viral hepatitis, but never in one of these studies.

So, for practical purposes, the numbers we get are 0, 1, 3, 4, and 6. It's a discontinuous score. I think that was because the authors originally tried to weight it as to what they thought was the biologic potential of these lesions.

Now, the other component of the injury is the

parenchymal injury, what's going on away from the portal areas, and that's where liver cells undergo apoptosis through some mediated immune mechanisms. Lymphocytes again come in contact with the liver cell and cause it to degenerate, activate its suicide genes, fragment, and undergo apoptosis. After the cell is dead, then a cluster of inflammatory cells is left behind and that remains there for several days. So, it allows us to see how much injury has occurred recently.

The way to score this is to look at the entire section on low power, and you get a visual estimate of how many cells are undergoing degeneration necrosis. There's one there, one there, one there, one there, and then there are clusters of inflammatory cells showing where they have died. Again, you look at the overall biopsy and decide whether it's mild, moderate, or marked and assign a score based on that. That's for parenchymal injury and also for portal inflammation, which I won't show any more on.

Then we do the same for fibrosis. There they set up a scoring system based on how much architectural distortion there was. This was more in lines of more permanent forms of injury. If it's just portal or periportal scarring, that gets a score of 1. If there's extension of the fibrosis, fibrous scars from one vascular structure to another that is bridging, you get a score of

3, and when there's cirrhosis, you get a score of 4.

Then we add them all up and come up with the overall histologic activity index, which would have a maximum score of 22, but I've only seen I think, in my 18 years doing liver pathology, one case of viral hepatitis that had a score of 22. Really in practical terms the maximum would be perhaps 18.

Let me first mention that when we're looking at a large number of biopsies in the context of a study, the scores can be quite variable from the pretreatment to the post-treatment. One reason for this is the natural history of the disease. We know that chronic viral hepatitis is an episodic disease, that there are times when there's exacerbation of the disease and times when it's quiescent.

There's sampling variability. The liver is a 1,500 gram organ and when we take a liver biopsy, we're only looking at 10 milligrams of tissue, a tiny little part of it. Depending on the size of the biopsy and how representative it is, you can get variation in that regard. I've seen a good size biopsy where one end of the biopsy will have a score of 10 and the other end will have a score of 0. If you have only half of the specimen, that will affect the score.

There is some interpretation variability. At some point in time, one has to make a decision. Is this

mild or is that moderate? Well, that's a difference of 2 points right there, and depending on what you had for breakfast, that can affect the interpretation.

In the context of a large study, these should all cancel out. Some will go up and some will go down due to these random changes, and the overall effect will be 0. Then any effect that's left will be the effect of our experimental therapy.

So, let me show a few examples. All of these are taken from the 3010 study, the placebo-controlled trial.

On the left is the pretreatment biopsy and on the right is the post-treatment biopsy. So, here we have a pretreatment biopsy where there's some portal inflammation here, a little bit. There's a little bit of interface hepatitis and there's a little focus of parenchymal necrosis out there. That would get us an inflammatory score of 3.

Over here we have the post-treatment biopsy from the same patient and he's got quite a bit of inflammation here in the portal area. There's interface hepatitis everywhere where we have the opportunity to have it. So, we have a moderate degree of portal inflammation, a marked degree of interface hepatitis, and also a marked degree of parenchymal necrosis away from it. So, that

would get an inflammatory score of 11.

This patient happened to be on placebo, and so probably that's the natural history of the disease. In his pre-treatment biopsy, he was in a quiescent phase. Post-treatment he was in a very active phase with a difference of 8 in his inflammatory components of his score.

Here's a patient who happened to have been getting lamivudine. Here's his pretreatment biopsy and here's his post-treatment biopsy. Over here is a portal area with a great deal of inflammation, interface hepatitis all along the front here and spotty necrosis within the parenchyma. Here's a little portal area, which you'll see at higher power in the next -- the next slide will be a higher power of this area compared to this area.

Here's that portal area with no inflammation, really essentially normal parenchyma. Out away from the portal area, we can see there are lots of clusters of inflammatory cells and acidophilic bodies where there's been necrosis and dropout of liver cells. So, here we have a score of perhaps 11 pretreatment and a score of 0 post-treatment.

Another patient who was getting lamivudine. I should say parenthetically I didn't know this at the time I was scoring the biopsies. I didn't know which ones went with which and I didn't know what their order was. I just

had to do a score and then afterwards the code was broken.

This is pretreatment. We have portal inflammation, interface hepatitis all along here. Post-treatment here's the biopsy from the same patient, a different portal area, of course, because that one was taken out during the biopsy. Here's portal fibrosis here, a little bit of inflammation, and a little bit, at one focus, of piecemeal necrosis there. Quite a bit of improvement.

Another patient, pretreatment over here with spotty necrosis and inflammation. Post-treatment over here he has essentially normal parenchyma. Now, we'll back away a little bit, same biopsy. We are looking at this area and this area.

Here are two portal areas from that patient. This one is quite expanded with a little bit of inflammation but a lot of interface hepatitis all around it. The same thing over here. Here's a portal area here which looks essentially normal, quite a difference in the inflammatory activity.

Now, we're going to move on to fibrosis because that's something else that was scored, and after scoring it, then I went back and looked at these in pairs to do the ranked assessment. So, notice this portal area here, and this one will be in the same place on the next slide and

this one will move down a little bit so we can bring another one into view.

So, that's the same biopsy. The blue stain represents collagen. This portal area is expanded, so is this one. Over here we have that portal area that has virtually no fibrosis. This one up here, it was on the edge of the section, but it has just a little bit of fibrosis. So, in the Knodell score, these would each get a score of 1, but you can see there's a difference between the pretreatment and the post-treatment. Dr. Brown talked about worsening of fibrosis, but actually in this case the fibrosis got better.

And I'll show a couple more examples. Here's another one. These are all where the fibrosis got better. Pretreatment there's bridging fibrosis here. Post-treatment it's a little bit dark but a couple of portal areas with just a little bit of portal fibrosis. Now, some of this could be sampling, of course, but overall there were many more that improved in the lamivudine treated group than in the placebo treated group, and on the other hand, in the placebo treated group more of them went the other way.

And one last slide showing quite a bit of bridging fibrosis here in the pretreatment and still some bridging fibrosis but much less in the post-treatment.

So, some of this of course could be sampling variability. I don't think it's all interpretation variability. Some of it could be the natural history of the disease, but when you look at the overall cohort, there's obviously an effective therapy.

So, now I'll turn it back over to Dr. Brown for questions.

DR. HAMMER: Nothing more formal. Okay, thank you.

I'll just rewind the tape to my previous comments. We're going to go around the table to ask some questions. We have limited time today and we'll have more time for questions this afternoon. So, I'd ask you to prioritize your questions and just ask your top one, two, or three questions in deference to your colleagues. I'll start on my left with Dr. Fletcher. Do you have any questions for the sponsor?

DR. FLETCHER: Thank you. My question concerns for patients that may take lamivudine for hepatitis B how truly confident we are that 100 milligrams a day is the optimal dose. The pharmacodynamic modeling indicating the plateau effect, while compelling, is done from short-term studies at approximately 1 month, but the peak clinical effect doesn't seem to occur until at least 6 months or so of therapy. So, given the safety profile of the drug, how

do we know that a larger dose would not produce a response in a greater number of patients for a more prolonged period of time?

DR. BROWN: We should have a slide shortly on that issue, M-87.

These are the principal findings we've had in the program with regard to the dosing effects of lamivudine in hepatitis B patients. I mentioned the phase II dose-ranging effects, but I think as was just mentioned, those were relatively short-term treatment periods.

The phase III study, the Asian multi-center study which included the 100 milligram 1-year treatment cohort as well as the 25 milligram treatment cohort, showed a superiority for the 100 milligram cohort over the 25 for sustained HBV DNA suppression.

I should mention we have some PCR data from two different studies. I may have mentioned it briefly. They would indicate, just as we saw no difference for doses above 100 milligrams per day, we saw no difference for HBV DNA reduction or clearance, if you will, in the standard assay. When we looked at PCR data both in adults and children, we found no difference in proportion of patients who clear by PCR for doses above 100 milligrams. Those explored doses to about 300 milligrams essentially.

So, we have some limited PCR data to support

the notion that we have the dose at which one achieves a maximal antiviral effect. Doses above that really would be difficult to distinguish an antiviral effect without infinite sample size essentially because of the existing data suggesting no appreciable difference within the program.

Of course, one of the key things that dose may play into is the whole issue of the incidence of the variants with reduced susceptibility. That's kind of a traditional issue in antiviral therapy.

Importantly in this program, we saw no difference in the incidence of YMDD variants in the large multi-center Asian study. We saw no difference in the incidence of YMDD variants in the 25 milligram or 100 milligram cohort, even though this cohort had a superior antiviral effect. The incidence of variants was indistinguishable in these two cohorts at a year, and as well we did a fair amount of regression modeling to look at the issue and we didn't see any dose effect there either. So, although it might be reasonably expected that there could be a dose effect, our data does not suggest any appreciable advantage for doses above 100 milligrams.

I should mention parenthetically -- it was actually in Dr. Dienstag's publication of the U.S. 3-month study and also in a publication in the Annals, in a letter

to the Annals in April, doses above 100 milligrams will actually produce a little quicker reduction in HBV viremia, but the proportion of patients who've cleared does not appear to be different and that's an important thought I think. So, we figured the long-term clinical significance has more to do with where do patients get to and what proportion of patients clear, and in that regard, we've seen no difference, no advantage for doses above 100.

DR. HAMMER: Ms. Melpolder, do you have any questions?

DR. BYE: Could I just make a supplemental comment on behalf of Glaxo Wellcome?

DR. HAMMER: Please identify yourself for the transcript.

DR. BYE: Dr. Bye, Glaxo Wellcome, Clinical Pharmacology.

It's a very interesting question, and what we've found, there was remarkable concordance between the acute model and the long-term chronic therapy, and there was a population analysis done from the data that Dr. Brown was alluding to where we had pharmacokinetic sampling. And we also found this relationship in terms of AUC and effect of around about 4,000 area units.

DR. HAMMER: Thank you.

Dr. Hollinger?

DR. HOLLINGER: Yes. I'd like to, first of all, just comment about the reduction that you were just discussing. With viruses, when you've got hundreds of billions of particles that can be circulating, 99 percent is not a great deal. I mean, it's a fair amount, but you're still left with a very large amount of virus in that population. And that has always been one of the things that has concerned me because the hybridization techniques which are often used have a cutoff somewhere around 5 million or so, whereas PCR techniques may be down to less than 100, less than 50 copies per ml. So, I think that that's something that needs to be assessed a little bit better.

On the other hand, there may be a cutoff level at which levels have a great deal to do with improvement in histology. It seems to be that way. Could you comment, first of all, about that? Then I need to ask you something else.

DR. BROWN: Sure. I mentioned we had two sources of PCR data. One was in the European 6-month phase II study, kind of our last phase II dose-ranging. We did do some PCR analyses in that. There we found no real difference in proportion of patients who cleared -- detectable virus at PCR levels of sensitivity at 6 months, and the dosing cohorts there were 25 milligrams, 100, and

300. So, even at PCR levels of viremia, we didn't see a dose effect, so to speak.

What we did see, however, is when we look at the PCR data we have, as well as the branched DNA data that we have from the pediatric study, we see that on average the viral load reductions with lamivudine, in fact, tend to average 3 to 4 logs. So, it's well over the 99 percent.

I mentioned in the data displays you saw, we were kind of artificially limited to a 2-log display because for the purposes of those analyses, just for manipulating the numbers, we arbitrarily assigned an undetectable value. We assigned it a value of .8 picograms not knowing what the real viral level might be, of course. So, in fact the antiviral effect is more like 3 to 4 logs, what you might call 99.9 percent on average.

DR. HAMMER: If I may, what's the lower limit of sensitivity on the PCR assays?

DR. BROWN: Yes. We were using an assay that typically had a sensitivity of 1,000. Some labs will advertise 10 or 100. We feel we had a consistent 1,000 detectability.

I'm not sure if I answered the entire question. If you would remind me of the second half of your question.

DR. HOLLINGER: I saw that in here where you said you used .8 picogram. I was under the impression that

1 picogram --

DR. BROWN: .8 picogram.

DR. HOLLINGER: -- is about 300,000 copies per ml.

DR. BROWN: Right.

DR. HOLLINGER: Yet, the hybridization assay has a lower level of detection of 5 million. So, I'm not sure why .8 was used instead of more than that.

DR. BROWN: That was just a convention we adopted. The threshold of detection, the lower limit of detection of that assay is thought to be on the order of 1.6 picograms per ml. So, we arbitrarily assigned a value of half that to the undetectables.

DR. HOLLINGER: Yes. Again, I'm not sure why 1.6. Maybe somebody could help me. We've always used that 1 picogram was around 300,000, so 1.6 would be around 500,000, not 5 million which would be closer to 10 picograms in there.

DR. BROWN: Right. The kit had a fair amount of data behind the kit to suggest a threshold of 1.6 picograms. I think you're also alluding to a problem in the area of HBV diagnostics in general which is that there's no real cross standardization, and in particular there are no real known gold standards for serum samples with defined viremia levels by particle counts or some

traditional method.

DR. HOLLINGER: Scott, if I could ask one other.

I think safety is really a key issue here, probably as much as anything. You know the problem with fialuridine and its effect on mitochondrial DNA. I know you mentioned in your information -- very good, by the way. The packet was very nicely put together and very useful.

You mentioned about the fact that this is only transiently incorporated into mammalian DNA and that any amount that might be incorporated into the DNA would probably be removed by a 3 prime/5 prime exonuclease activity. Can you go a little bit more into that and tell us why that's the case and what information you had to support the fact this does not act as a chain terminator of the mitochondrial DNA?

DR. BROWN: If we might have slide M-75. This kind of summarizes the data for why we feel there are no fialuridine-like effects with lamivudine. I think one obviously would keep in mind as well that fialuridine-like toxicities, if they're mediated by mitochondrial damage, would of course be appreciated as general toxicities that would occur fairly commonly in a patient population and, as was seen with fialuridine, might occur with cumulative dosing, but it wouldn't be a rare kind of event because

mitochondrial DNA and mitochondrial proteins are well conserved across individuals with minimal polymorphism.

So, in any case, the observations that are relevant for lamivudine are, first of all, that the drug has negligible affinity for gamma-DNA polymerase and no 3 prime hydroxyl group, and that's what results in the no stable incorporation into mitochondrial DNA.

We have done studies and especially a number of external investigators have actually studied lamivudine and other nucleosides with regard to their effects on mitochondrial function, such as glycolytic pathways and oxidative pathways, and lamivudine has been noted, I think in the New England Journal editorial and a few other places, to have no effects on mitochondrial function. In fact, there was a literature report I guess this past June by the Dutch group suggesting that KICA breath testing in hepatitis B patients may actually be improved on lamivudine therapy, and that is thought to be a measure of mitochondrial function.

In any case, we've also had some in-house data, in animal based data, that there were no ultra-structural changes in mitochondria in animals treated chronically with lamivudine.

The clinical evidence actually, first of all, is that there's no fialuridine-line syndromes observed in

the clinical program, no cases of clinical pancreatitis observed in the phase III control data. That may be important. I showed you the data that amylase, lipase, and ALT elevations were similar to placebo. I'm mentioning this because the full-blown fialuridine like syndrome, if you will, comprised pancreatitis, acidosis and elements of liver failure sometimes. So, these are the clinical observations, again backing up the notion that we really don't see any fialuridine-like effects with the drug, but we think these are scientific reasons.

DR. HAMMER: Dr. Sjogren, do you have questions?

DR. SJOGREN: Thank you, Dr. Hammer. I have a couple of questions for the sponsor.

The first one is in patients who received lamivudine for a year, maybe 2 years, and there is no e antigen loss, does the sponsor have a feeling for what happens -- how long can we continue giving lamivudine, especially in patients who may be quite compromised and in which a recurrence of hepatitis B could be quite significant in their clinical outcome?

What is the experience in this kind of patients if you stop lamivudine? What is the experience long term? What happens to them clinically and histologically? Do they know?

DR. BROWN: This is kind of a limited clarification period, so I won't show you the slides with all the data, so to speak, but let me just mention.

We've actually looked at the data for patients, for example, in the composite phase III who did or did not lose e by week 52, and there's clearly a histologic benefit in the patients who don't seroconvert, if you will. We do see histologic improvements in the patients who are still e positive beyond a year, so to speak. So, I think the answer to the first part is we expect to see improvements in liver histology and ALT normalization in those kind of patients on a prolonged basis.

I showed you the end of year 2 data in the longest cohort we have, which is the Asian multi-center cohort, where approximately 40 percent of the lamivudine patients had developed detectable variants. If you look within that group at year 2, at week 104, 60 percent of the patients with the variants have normal ALT levels, again some evidence that there will be prolonged benefit obviously with the wild-type that tends to stay suppressed, but as well with the variants. I should say the ALT normalization rate after 2 years in patients with wild-type was 80-plus percent.

So, we think patients who don't e convert will continue to have benefit in their liver disease measured

histologically, also by ALT levels, and I hope that is a substantial answer to your question.

DR. SJOGREN: Another question that I have is it was mentioned that patients with normal ALT were included in one of the phase III trials in the Orient. I wonder if they were able to analyze that data and what kind of conclusions did they draw in patients that have normal ALT and what happens to them.

DR. BROWN: Yes, it's certainly possible that the discussion may range over these in the afternoon where you'd want the color slides, but in a nutshell, in patients with normal ALT what we found in this trial program was that the median -- as you mentioned, the cohort is derived essentially from that Asian multi-center trial. It's about a third of the patients in that cohort.

The median HAI score at baseline for the subgroup with normal ALT was 5 points. Zak has sort of told me indirectly that any one of us might have score up to about 3, but 5 is probably abnormal. We were able to measure histologic response in 44 percent of patients with normal ALTs. So, a patient who just has one cross section of value at normal ALT may not represent the true, healthy, long-term healthy carrier, and there's literature from the late 1970s to suggest that if you just have a cross sectional analysis of a population and look at people with

normal ALTs, roughly 40 to 50 percent of the patients will have some underlying liver inflammation. I think that data is very similar to what people have found in hep C blood bank based studies.

DR. HAMMER: I'll just interject if there's a key slide that you wish to show to answer questions, please do.

DR. BROWN: I gave the numbers off the key slide.

DR. SJOGREN: What about e antigen loss in that kind of patient, in the ALT normal? I understand that histologically it may be difficult to make a very clear point as compared to your chronic hepatitis patients, but the e antigen loss in those patients -- what did it look like?

DR. BROWN: Right. We've done some subgroup analyses and some regression modeling. You do see higher rates of e antigen loss progressively with higher and higher ALTs, just as you do with interferon, although I will say the association with lamivudine may not be quite as tight because it's not always a statistically significant association. But even in the low group with less than twofold elevations at baseline, we do see a rate of e loss that may be a bit above placebo. The actual numbers, at less than twofold elevation, I think it was 12

percent. This is the histologic response I mentioned earlier, but 11 to 12 percent of patients with ALTs below 2 will lose e compared to a placebo rate of 5 percent. So, with large enough studies, you probably could measure an effect. With absolutely normal ALTs, e conversion probably is the factor that's most influenced.

DR. HAMMER: Dr. Lee.

DR. LEE: Thank you, Mr. Chairman.

I'd just like to make a comment about one of your key phase III studies and then ask for your responses.

The B3010 active control study. First of all, the histology appeared worse in the combination group treated with lamivudine and interferon than lamivudine alone, but I think the timing of the second biopsy done while people were still on lamivudine treatment versus in the combination group, having been off treatment for 28 weeks, makes that data very, very difficult to interpret. It would only be logical that someone still on the active treatment would have a much better histology.

The second thing is I think many of us in the hepatology community were disappointed at the outcome and the design. It appeared that the 29 percent e antigen seroconversion rate in the combination group might have been statistically significant if the study had been sufficiently powered with a bigger sample size. Certainly

I remain unconvinced that the combination isn't the way of the future, and I'd like to hear the company's comments.

DR. BROWN: Sure. Maybe we should start with slide M-35.

This is the direct comparator study, which has just been referred to, the European/Canadian multi-center study. Here we're showing not just the proportion of patients whose histologic activity index improves by 2 points or more, but also the proportion of patients in whom it worsens by 2 points or more, indicated down here. The other patients are patients whose change in HAI score was less than 2 points, and those would be on the 0 change line. So, let me first comment on the sort of histologic differences, if you will.

We showed you in a sense the above 0 change line results on previous slides in this particular display instead of the conservative display of all missing data's nonresponders. We just excluded them from the analysis.

So, here you see the results for lamivudine monotherapy on that trial for the reduction in Knodell HAI score. You see the actual distribution of change, if you will, by 2-point categorical changes clearly shifted in the right direction for lamivudine.

This is the interferon monotherapy arm here where just speaking arithmetically, so to speak, a higher

proportion of patients on interferon monotherapy seemed to worsen.

This is the result you alluded to. This is the distribution of histologic change in the combination arm for the overall change in total HAI, a bit of a shift above the 0 change, but not as impressive as perhaps either of the other two.

So, what does this say? It doesn't necessarily mean that more patients worsened. It just means that, in a sense, in this particular study fewer patients improved.

Here's the change in fibrosis, and this is sort of the distribution of change in fibrosis. This is done by the so-called ranked assessment because we felt that the discontinuous 4-point scale, so to speak, in the Knodell might not be the right way to go in this kind of analysis. So, these are the blinded ranked assessments that Dr. Goodman alluded to. It looks at both slides and arbitrarily decides -- or I should say studies the slide and decides which slide looks better and assigns a score to that, and then which slide looks worse, and then unblinds treatment eventually in the end once all the readings are done.

What we see here is for the prevention of fibrosis -- or I should say for the proportion of patients who have improved in fibrosis versus worsening. We showed

you some of the worsening comparisons. In particular, in this study the comparisons of lamivudine to the other two treatment arms -- there was a trend in a sense. The 3 decimal p value of this comparison was .051, but that was not a statistically significant result.

Here's the fibrosis result for the combination.

So, my sense of this data is there's no clear advantage histologically for combination.

I should briefly mention the other principal results from the study.

For ALT normalization, ALT normalization was significantly best and significantly better for lamivudine monotherapy compared to either interferon or combination. So, yes, the e loss and e conversion rate, so to speak, which you saw in the slide were a proportion higher, but they were not statistically significant in the intent-to-treat and there were some disadvantages or lack of other advantages for combination. But I think we all agree that combination regimens in the right setting and perhaps other kinds of designs in the future with interferon even might be worth studying. But this particular design did not produce any clear advantage, and of course, there were some safety offsets that I did review.

DR. HAMMER: Dr. So?

DR. SO: Thank you, Mr. Chairman.

I have a few questions. The first one is can you comment on your incidence of loss of B surface antigen at 1 year and 2 years? Because based on the information you have provided on the book, I made some quick calculations, and it seems like at the end of 1 year patients who were treated on lamivudine had an incidence of B surface antigen loss of 1.5 percent, whereas the patients who were treated with lamivudine and interferon, the incidence was 3.4 percent at 1 year. Do you have any further information?

DR. BROWN: Yes, slide M-49.

This is the overall observation regarding s antigen loss, which I think we're all interested in because it may represent in a sense ultimate clearance of the virus, although even patients who are anti-s positive and have never had active disease can be reactivated under conditions of debilitation. So, s antigen loss is not a perfect marker of cure, but it's pretty good.

This is the overall s antigen loss observation for phase III. If you look at the sort of comparative data, the direct comparison was in that European/Canadian multi-center study. What we saw was 3 patients on lamivudine 100, 3 out of 82, lost s. On the combination arm, it was 2 out of 75, and on the interferon it was 2 out of 69. So, indistinguishable in the head-to-head

comparisons at 1 year.

There was sporadic s loss elsewhere in the program illustrated here.

Perhaps interestingly, even though I think the bottom line on this has to be that the s loss numbers are quite low across the program, but perhaps interestingly there were no patients treated with placebo throughout phase III who lost s, and all the sporadic s loss occurred on the other treatment assignments.

But if you take these kind of percentages in parentheses for the various treatment assignments and in particular probably the most important thing is the head-to-head comparison. These are the treatment-naive studies, by the way, and this is the interferon nonresponder population who may in fact have some biologic differences. But in any case, we didn't see an appreciable treatment-related difference, and obviously to statistically measure any differences there would need a very large sample size.

DR. SO: What about the 2-year follow-up in the Asian study?

DR. BROWN: Well, actually interestingly enough, I didn't point it out here, but as you might have guessed from the New England Journal article as well, it did appear that s loss was a bit more common in the sporadic observations that we had. There was actually no s

loss in the first year in the Asian multi-center trial published in the New England Journal.

Actually, I might turn to Frasier. I don't know if we have any s loss in year 2. So, it's still low or 0 in year 2 we think.

I didn't actually mention this. We could get into it this afternoon. What we see in Asians versus westerners, there's a similar full e conversion rate at 1 year, but a little higher e loss rate at 1 year in the westerners. There may be a subtle difference here in s loss where the sporadic kind of s loss we see may be a little more common in western populations. That would be actually sort of similar to what you might expect from a reading of the epidemiologic literature on just patients who naturally e or s convert.

DR. SO: So, as Dr. Lee said, I think it's still worth studying the effect of combination therapy with interferon to try to increase the incidence of surface antigen loss in that population.

DR. BROWN: Right, and we'd probably agree.

DR. SO: The other comment is you mentioned you were thinking of using hepatitis B e antigen seroconversion as a target endpoint for treatment.

DR. BROWN: Right.

DR. SO: I guess this is based on the European

long-term follow-up of patients who were treated with interferon, and after 5 years, patients who seroconverted seemed to have a lower incidence of complications of cirrhosis or hepatocellular carcinoma. Is that right?

DR. BROWN: Are you referring to the Niederal paper in the New England Journal?

DR. SO: Yes.

DR. BROWN: Yes. I think the principal finding out of that was that e loss was, in terms of the data they could measure, the variable that was most associated with better long-term outcomes.

DR. SO: I have some concern from my colleagues in Asia, especially from Hong Kong, where they followed close to 1,300 patients with chronic hepatitis B, and they found about 68 percent of the patients who eventually developed complications of cirrhosis such as bleeding, ascites, and also hepatocellular carcinoma were actually anti-HBe antibody positive.

So, the endpoint of treatment may be much further than just seroconversion. I think you really need much longer follow-up and treatment to assess whether it makes an impact on lowering the incidence of complications of cirrhosis or reducing the risks of hepatocellular carcinoma.

DR. BROWN: Right. You may be referring too to

a clinical phenomenon, the so-called precore mutants, where patients with precore mutant virus, of course, can be e negative/anti-e positive, but in fact have high viremia levels or middle to high viremia levels, I should say. What we've run into in running this development program is that the data on precore mutants appears to be a lot more extensive in southern Europe, for example, than it is in Asia, although you can see in the literature that precore mutant or anti-e positive hepatitis B is in fact thought to be reasonably common out there. We're actually doing a kind of an epidemiologically based molecular study, if you will, to try to look at the prevalence of precore mutants.

But that phenomenon of a patient with active virus replication who's anti-e positive is often due to precore and core gene mutations in the virus which don't seem to affect its pathogenicity. Some studies suggest it may even be a little worse.

We did conduct a study in Europe in about 126 patients with precore mutant hepatitis B, and that result was actually reported in the spring. The antiviral effects in those patients appeared to be quite good. The difficulty there is you can't measure e loss because they've already lost e. So, that kind of phenomenolgy is mixed in with the other phenomenon that you're referring to I think which is some patients will develop advanced

disease and may seroconvert around the same time, and so they can seroconvert. But it happens to have happened or may even accelerate in some cases their cirrhosis development. That kind of patient can have a poor outcome even though they're anti-e positive.

DR. SO: Actually the study I refer to is from Hong Kong, and they found that about most of the patients in that population -- if they seroconvert to anti-HBe antibody positive, they were like at a median of 35 years of age, and they developed complications of cirrhosis and hepatoma at the age of about 43 years of age.

But since the primary target population is going to be a lot of Asians, just shooting for target endpoints for seroconversion might not be adequate. It might have to be given long term to really see whether it makes an impact.

DR. BROWN: Yes. Certainly we're going to be looking at some long-term benefit and have designed a fairly substantial, what we hope will be a phase IV study to look at long-term clinical benefits.

The way we try to differentiate those patients who are anti-e positive and what their outcome might be is to use DNA assays. A lot of the patients with precore mutants will have detectable DNA, whereas the patients who are going to do well will be the patients who are e

negative but also DNA negative. That's in fact why we linked the DNA analysis into our e conversion. In a sense, it serves as a way to screen out patients who may have developed precore mutants.

DR. HAMMER: Thank you.

Dr. Stanley?

DR. STANLEY: Thanks.

Just a quick follow-up to Dr. Lee's concerns about NUCB3010. Not only are you comparing patients being treated with those off treatment for a while, but the combination patients only got 24 weeks of lamivudine compared to the 1 year. What was the rationale for that?

DR. BROWN: I should first thank Schering Plough for supplying the interferon alfa-2b.

That was actually a design that was used in the U.S. multi-center trial. The feeling on if they got interferon treatment was that the maximum benefit in B -- and this may or may not be true for C -- so, there are differences in these two hepatitises. But the maximal benefit in B with interferon therapy does not appear by end of treatment. It actually appears that patients will continue to experience some seroconversion out to about at least 6 months post-treatment.

So, if you look at the design of the U.S. multi-center trial that Dr. Perrillo published in the New

England Journal or if you look in the U.S. label for Intron A, you'll see that in fact the primary assessments for both virologic response and histologic response were 6 months post treatment. The feeling is at the end of treatment -- and Dr. Perrillo is here, if you want to comment -- many of the good responders to treatment may actually be histologically flaring. So, the histologic results at end of treatment in B are not necessarily as good on interferon as they are 6 months later. So, that was one of the main reasons I think why the advice to put the primary assessment 6 months post-treatment for interferon was incorporated into the trials.

DR. STANLEY: But I'm specifically asking why the lamivudine was limited to 24 weeks because you've shown in other patients that post-lamivudine, they may have a bump in ALT anyway.

DR. BROWN: Right. That's a scientific design question. I mentioned briefly that really what we were trying to investigate there was, does pre-reduction of viral load with lamivudine for 8 weeks allow an enhanced seroconversion rate with the interferon, and we wanted, of course, keep viral load low during the interferon treatment as well. That relates back to some data that Dr. Perrillo and others published that patients with viral loads above 200 picograms or so don't respond well to interferon. So,

the thought really in this collaborative effort was that if we pre-reduced viral load, we may get enhanced seroconversion.

I think the designs that many people are thinking about nowadays are to continue lamivudine and piggy-back an interferon and see if that might produce a better effect. We don't have that measurement available.

DR. HAMMER: Thank you.

Dr. Yogev.

DR. YOGEV: Thank you.

I would like to ask a couple of questions about the pediatric and adolescents. First of all, how many adolescents were in the studies?

DR. BROWN: Let's see. We have that number, but it might be easier just to get it from somebody who has got it memorized. There were 53 total patients. How many adolescents? 14 or 15. We could dig it out of the slide if you need it.

DR. YOGEV: The reason I'm asking is at least from data you submitted, it seems like that they did not respond as expected in a dose which is the adult. They were much less good. Any explanation for that? Are you planning to do more adolescents?

DR. BROWN: Right. Actually their response was quite good and I think we can show you that response. I

think we have it coming shortly, the pediatric DNA response.

This is some data from that study. This is actually the baseline DNA and ALT in the dosing groups in the pediatric study. I think what we want to do is skip ahead to the DNA response graph.

The primary virologic method in this study was the branched DNA assay, although we did also do PCR as well. We haven't unfortunately broken out the adolescents, but here you can see the similar kind of very marked antiviral effect at 2 weeks, patients essentially clearing in the Chiron assay. I don't recall there was a substantial difference for the adolescent patient subgroup, but perhaps Dr. Dent or Dr. Gray would want to comment briefly.

The next slide may have the log decrease. Yes. Again, but this is not broken out by adolescents. I'm sorry. There it is, the 100 mg dose, yes. Essentially this is probably due to fairly small sample sizes and sampling error. I don't think we appreciated that it was a significant difference, if you will.

Here's a good example of the kind of phenomenology that Dr. Hollinger alluded to in some respect. Using a more sensitive assay with a wider dynamic range, we do see a 3 log reduction on average, but that's

using a more sensitive assay.

I think in these kinds of cohort sizes, these kinds of treatment differences -- using the AUC data and the antiviral effect, one can appreciate that through that kind of effort that there is a dosing difference. But in terms of proportion of patients who clear in adolescents as a subgroup, I don't think we really appreciate the significant difference because of the sample size.

DR. YOGEV: And the study was only for 4 weeks?

DR. BROWN: Right. This was a dosing cohort study. Actually I guess we can say we've initiated at this point a large phase III multi-center study in children, an international study in North America and Europe.

DR. YOGEV: I noticed that you used the 2-point score of Knodell as the one to assure a major change. And yet, the hepatologist was mentioning that you can have that change. It depends what you eat in the morning. I just wonder, what would be the intra-pathologist difference? Would it be more than 2 or 3 points?

DR. BROWN: Yes. The typical change on the lamivudine treatment groups, the change in median scores for the group as a whole, was typically 3 to 4 points or more, but the change in median score was typically 3 to 4 points for lamivudine.

The 2-point categorical response definition is

essentially quite consonant with what's been recommended in hep C trials by the NIH consensus conference. The difference there is last year they recommended subtracting out the fibrosis score, if you will, and measuring changes in necroinflammatory response, the sum of the first three components. So, we did actually do that in our program, and I didn't highlight it on my slide, but there were significant changes in the categorical approach to that kind of data, using 2-point or greater change as recommended for hep C trials. But as I mentioned, this change in median scores tended to be on the order of 3 to 4 points, which might be more clinically --

DR. HAMMER: The question that Dr. Yogev raised about inter-pathologist variation, which came up in one of your studies?

DR. BROWN: I think, as Dr. Goodman tried to point out, when there's, if you will, that kind of subject of a random variation, that would actually obviate against observing a treatment effect in large trials. So, as Dr. Goodman pointed out, that's the power of doing large controlled trials, is to see this kind of treatment difference between two groups.

DR. HAMMER: Thank you.

Dr. Hamilton?

DR. BROWN: I should add one other comment.

I'm sorry, Dr. Hamilton.

The reason we adopted a categorical response definition goes back to some early trials where differences in means for response were thought to be potentially clinically meaningless. For example, in some of the early trials, there was a .7 difference in mean scores for treatment groups, and that was thought to be perhaps not terribly clinically relevant.

So, it was thought more appropriate to define some kind of categorical response that patients might achieve and might be clinically significant and then measure that as a categorical phenomenon because if you do very large studies, of course, relatively small differences in means may become statistically significant, and yet that may not be clinically significant. So, that's why you adopted these kind of categorical response definitions.

DR. HAMMER: Were the pathologists blinded to --

DR. BROWN: Yes.

DR. HAMMER: They were blinded to the treatment. Were they blinded to the patient over time?

DR. BROWN: Yes. In trying to cut down the data from 40 trials to a relatively brief presentation, I removed one slide that emphasized that these studies were all done with the central independent pathologist blinded

with regard to the slides, with regard to treatment, patient identification, date, and sequence. They didn't know which was the baseline and which was the follow-up slide.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: Yes. I'd like to reciprocate for the clinician-friendly slides by asking only really easy questions here this morning.

(Laughter.)

DR. BROWN: We are most grateful.

DR. HAMILTON: A nuts and bolts question first. I added up a few of the columns and a few of the rows on some of the slides to try to come up with a sense of lost to follow-up, missing pieces of data, dropped out, disappeared, whatever, and I didn't actually satisfy myself about that point. Could you speak to that point?

DR. BROWN: Right. In the overall program, we actually found that we had very good retention of patients. Typically at least 80 to 90 percent of patients completed the study. Overall, the highest study completion rate was in fact in the Asian multi-center trial. I think it was on the order of 96 percent. So, we had quite good patient compliance throughout these studies.

With regard to the impact on the data, probably one of the key slides to look at would be in the core, but

it would be the study, the subanalysis I showed of the 2-year Asian cohort carried forth for ALT and DNA data.

We've looked at that in some detail now, and that kind of stabilizing or trending downward, if you will, of the DNA and ALT values in the patients with the variants does not appear to be due to patient dropout. In fact, we lost 25 patients in that year of additional follow-on in the 3018 study. The reason we lost 17 of those 25 was that they were seroconverted and found to need no further treatment. So, 17 dropped out for e antigen conversion, and we looked at the 25 with regard to were they variants or not, and none of those were identified as variants at the week 52 analysis leading into their year of additional study. So, we don't think dropout phenomena account for that critical analysis that we showed you of the 3018 data.

As I said, in the overall program, the compliance of patients was excellent and a very high completion rate. If you look at the proportion of patients who actually got both biopsies, it was quite high compared to some of the earlier clinical trials in hepatitis B and C patients where as many as 30 or 40 percent of patients didn't have the paired biopsy comparisons. We typically had 80-plus percent of patients available with both biopsies.

DR. HAMILTON: A second question concerns the

possible difference, if any, in response in those patients who acquired their disease as adults or as infants. Having an Asian cohort, you might have an exceptional opportunity to examine that question, and I wonder if you did.

DR. BROWN: Well, some people in the room know I was trained as a pediatrician. So, the approach we've taken in pediatrics has been initially to emphasize those children who have active disease, not the kind of high viremic carriers that are found especially in the developing world. But I will say that the antiviral effects we expect to see about the same. We've taken an approach to active disease in children because we think those are the kids who most need it. As we evolve more and more lamivudine data, I think we'll appreciate what the effects are in what you might call high viremic children with normal ALTs who are quite common worldwide.

I don't know if that answers your question, Dr. Hamilton. That was your toughest question. You promised they'd all be easy, but if I can clarify that one, I'd be happy to.

Oh, differences in disease between vertical and horizontal?

DR. HAMILTON: Yes.

DR. BROWN: Yes, okay, sorry.

I alluded a little bit to our observations.

What appears to be the case in the integrated data set is that the e loss rate at 1 year is about 30 percent for caucasians, if we just limit ourselves so that we have defined ethnic groups. In caucasians, the e loss rate at 1 year was 30 percent compared to 20 percent in Asians, but if you talk about a gain of anti-e and, of course, maintenance of undetectable DNA, the seroconversion rate was not appreciably different between Asians and caucasians. So, it may be that we'll see a little higher seroconversion rate in the caucasians as they go into year 2, as they gain anti-e and that sort of thing. So, that was one subtle difference.

We did not see any difference in responsiveness to lamivudine with regard to histologic responses, for example, and there are colorful slides to show that.

We didn't see any difference with regard to ALT normalization. We have a number of regression models in which we looked at various safety and efficacy phenomena.

So, I would say the principal observations are a little higher e loss rate in caucasians compared to Asians at 1 year, but no real difference in seroconversion. I think the overall rate was something like 17 percent of Asians fully seroconverted compared to 18 percent of caucasians, not statistically different in the overall program. So, there may be something interesting going on

there.

DR. HAMILTON: Finally, in adults with acute disease, do you have any data?

DR. BROWN: No. The real problem there we run into I think is one I think everybody can appreciate. Especially in the West, the clinical recognition of acute hepatitis B is increasingly rare, and so it's extremely difficult to set up kind of a large-scale controlled protocol designed to find those patients.

The other key study design obstacle that we run into is trying to think about -- the primary endpoint would obviously be to try to prevent transition to chronicity or perhaps to have some impact on the acute disease. The latter is fairly easy if you can find the patients, but if transition to chronicity in adults is more like -- I think the more modern data would suggest 2 to 8 percent of adults might be chronic disease -- then trying to show a treatment effect on a 2 to 8 percent event rate requires very, very large sample sizes in a patient population that's difficult to find in the first place. So, that's why we haven't yet really been able to study acute hepatitis B although we have some goals to try to figure out a way to do so, perhaps through large networks.

DR. HAMMER: Thank you.

Dr. Diaz?

DR. DIAZ: It's a little bit different question but along the same theme. Within a particular study, were you able to in any way look at the placebo group compared to the treatment group and break it down in terms of length of time patients in each of those groups had chronic disease, in other words, how long they had changes, for instance, in their ALT over time, how long they perhaps had had other maybe histologic evidence of disease and compare those two?

DR. BROWN: Right. We did have a question in the case rec forms having to do with what you might call recognized duration of disease, and we didn't really see any substantial differences in that in across treatment groups.

The real problem with this kind of data might have been highlighted by that baseline -- I guess it was the disease-associated phenomena I showed, the routes of transmission. It appears that worldwide the single most common route of acquisition is unknown. Most patients don't know when and how they got their hepatitis B, and therefore the duration of infection is unknown and, of course, duration of the underlying liver disease is, therefore, also unknown. But we did have a question of duration of recognized liver disease, and it didn't appear to differ across treatment groups. But since it didn't, we

can't really measure an effect. It's an important question.

DR. DIAZ: I realize the difficulties in sorting that out, but I wondered if you had any particular data.

DR. BROWN: We don't really because of those difficulties.

DR. DIAZ: Likewise, on a different theme, not being a pathologist, I too kind of struggle a little bit with a scoring system that has a lower limit of significance set at a change in 2 HAI and yet recognize the consensus panel felt that would be significant.

You had different pathologists scoring at different centers. Correct? Was there any attempt to switch slides amongst centers to validate scoring systems between pathologists or, more importantly perhaps, to have the same pathologist rescore the same slides multiple times to validate their reliability of coming up with the same score or within 1 HAI score?

DR. BROWN: Yes. We certainly initially took kind of an exploratory look with -- Dr. Goodman may recall -- I think it was 25 or 50 slides. There seemed to be a reasonable correlation in a two and three pathologist comparison, but it certainly wasn't in the very, very tight range and that's very typical of what you see in the

literature.

So, the most important way in a sense to eliminate observer variation is to have an independent pathologist for each study and have them evaluated not at local pathology labs, so to speak, but by somebody who's trained and experienced with the scoring system which, of course, is not one that's in everyday use in the clinic. So, that has I think been established in the literature as well as an important way to reduce variability here.

But the way to reduce inter-observer variability is again to have at least within the study one pathologist look at all the slides, and that's the route we chose.

But as you saw, actually in the comparison, we were actually rather surprised. I showed you the primary histologic response data for the three placebo-controlled studies, and that was two different pathologists I guess, and the rankings for both drug and placebo were amazingly consistent.

DR. DIAZ: Right. Just a couple of quick questions.

On the one slide that you showed for post-treatment ALT elevations where there was a difference between the lamivudine and placebo for ALTs over 3 times baseline or those that were over 500, in particular is

there any correlation between those post-treatment levels and pretreatment levels?

DR. BROWN: I think the answer to that is no, but we probably haven't looked at that rigorously enough.

DR. DIAZ: I'll save my questions.

DR. HAMMER: Dr. El-Sadr?

DR. EL-SADR: I have a couple of questions. I think the first one that probably has a very simple answer is, why do we use this drug twice a day in HIV and once a day in hepatitis B?

DR. BROWN: Well, that is a very interesting question. I think somebody like Dr. Hollinger who is both a clinician and a virologist could perhaps reflect on this as well.

But what we think is happening is, first of all -- we actually published, based upon some of the early phase II data, a paper in PNAS in collaboration with some Oxford statisticians. In the UK project, we published a paper on the viral dynamics of hepatitis B, and sort of by implication, in comparison to HIV. So, hep B is a rapidly replicating virus, as everyone knows, but overall probably slightly slower than HIV. It probably has a little longer half-life in the body, not very long but a little longer than HIV.

If you combine that kind of virologic

phenomenology with the long intracellular half-life of the drug and the reasonable serum half-life, the long and the short of it is, when we measured HBV DNA effects with b.i.d., once daily or twice daily dosing, in phase II -- I didn't highlight that, but we didn't actually see a difference in terms of our ability to maintain undetectable DNA levels.

Then Dr. Bye and Dr. Johnson, our clinical pharmacologists, have done extensive modeling, and we feel that even with this kind of once-a-day dosing regimen, we can maintain drug levels in the trough that are consistently above the IC50 of the virus. So, that's another aspect of our dosing regimen, if you will, is to try to keep the levels above the IC50 of the virus, but we can do that with once-a-day dosing. The clinical observations are there was no difference between b.i.d. and q.d. dosing.

DR. EL-SADR: That's in short-term studies. Right?

DR. BROWN: Well, this was actually, sure, up to several months of dosing. The principal observation was at 1-month dosing. That's correct.

DR. EL-SADR: The other question is going back to I think Dr. Hamilton's question, you implied that about 20 percent or so of patients had missing follow-up liver

biopsy for your primary endpoint.

DR. BROWN: Correct.

DR. EL-SADR: Was that equal in the placebo and the active group?

DR. BROWN: Right. It was essentially equal across treatment groups. We actually did a number of analyses to look at that, as well as adjustment for baseline covariates, and there was still a highly significant histologic effect, if you will in the phase III data.

DR. EL-SADR: Did you try to look at this by sort of assigning the missing biopsies as failures or something?

DR. BROWN: Yes.

DR. EL-SADR: The same question I have as well for the other parameters that you looked at for efficacy because it seemed like all the missing data are imputed as last observation carried forward.

DR. BROWN: Well, let me mention two things. I thought the slide I showed in the core for the primary histologic response was with missing biopsies counted as nonresponders. It was in the core, but it was a little subheader that I didn't feature when I reviewed the slide. But in fact, the data you saw was with missing biopsies counted as nonresponders. Here you see it here.

DR. EL-SADR: It says here in the one we have that patients lacking either biopsy were excluded. Oh, I see. That's a different one.

DR. BROWN: This is the primary response in the placebo-controlled. Histologic response was the primary endpoint in these three studies. In this display, all the missing data, the patients are counted as nonresponders. It was actually significant in both analyses in terms of the statistical testing.

The other question actually is an interesting one. We did adopt some conventions for two serologic parameters, e antigen and s antigen, adopted the convention of last observation carried forward. Working with the agency, we also did some additional analyses without that convention. I don't want to presage their discussion, but our sense of those analyses was at least that the effects on e conversion were still there even when you did not have the LOCF conventions.

DR. HAMMER: Dr. Masur?

DR. MASUR: Do you have data on the safety of the drug in patients with more advanced disease or more active hepatic inflammation?

DR. BROWN: Yes. We have the four transplant studies that I mentioned, and we also have a fairly large number of patients on open label compassionate use. The

real problem in that setting, as you can imagine, is getting control data. When patients have really immediately life-threatening disease and there's no other agent approved in this kind of clinical setting, it's very hard to get control data. So, I mentioned that we do see more adverse events and more serious adverse events in this population, but when we looked at the pattern, they appeared to be the kind of events you see with the underlying severe liver disease or the surgical complications or immunosuppression. But we can show you all that data, but again it's uncontrolled safety data, kind of observational stuff.

DR. MASUR: Just to follow-up on Wafaa's question, maybe I didn't follow exactly what you said, but if the half-life of virus is about the same between HBV and HIV, the intracellular half-life is about the same, for some reason you use 150 milligrams twice a day with HIV. I'm just intrigued as to why there's a difference of approach and whether or not the frequency of resistance might be different with a different dosing regimen or a different dose, if that's clinically important.

DR. BROWN: Right. The ability to model half-life, of course, the only ideal way is if you had some kind of therapeutic intervention that would immediately, totally shut down virus replication for HIV or HBV. Those kind of

agents still aren't available. The kind of agent you saw here and triple therapy in HIV certainly pretty quickly does so, but as you know, the limitations of these half-life measurements start with that.

Accepting that, our modeling efforts so far are that HBV might have a half-life on the order of a day, day and a half, compared to half a day or day or so for HIV. So, that's why I mentioned somewhat shorter.

I think the bottom line is within the scope of this clinical program, which is quite large and quite lengthy with regard to some of the study periods, we haven't been able to see a dose effect within the range that we've studied. A dose effect on the incidence of variants, I should say.

DR. HAMMER: Thank you.

I just have one question. I'm struck by what seems to be a very consistent DNA response, antiviral response, but even after a year of treatment, moderate but proven histologic responses of around 50 percent or so, but even lower serologic responses. I was wondering if that's just a matter of time, or is there something else about limited potency which in fact may be evident by the fact that mutants do emerge?

And part of this, if you have the slides on DNA response and also with inter-quartile ranges because one

thing we haven't seen -- we've seen median responses, but we don't know whether there are some patients who respond with 4 or 5 logs and others that respond with 1 log or less. That may help explain the response rates we're seeing.

DR. BROWN: Okay. Let me try to distill this one a little bit.

We don't have a quartile display of response, but in terms of the antiviral response, we do see, as you mentioned, a very consistent initial antiviral response. HBV DNA reductions are essentially observed, as far as we know. Every patient we've been able to study has had an initial reduction. If they had an appreciable DNA level, they've had an appreciable reduction.

There is a range in terms of the quantitative reduction in that initial antiviral response. It's relatively unusual for patients to not clear below detectable in the solution hybridization assay, but there is a small proportion of patients who don't.

Most of the patients are down in the range of detectability alluded to by Dr. Hollinger, in sort of the PCR range. Dr. Condor and I occasionally discuss this, our project virologist. There is some variability in that range in terms of patient response, but it's relatively unusual to not clear by the conventional assay.

I should say, as was alluded to earlier, that risks for disease progression in the existing literature so far are primarily -- I think Dr. Hollinger actually alluded to this issue -- associated with levels of viremia that are detectable in conventional assays. So, differences in PCR level viremia in HIV are important because there obviously the max studies have shown, even low level virus, you may eventually progress.

But in hepatitis B, Dr. Hollinger alluded to the issue that there may be a level of viremia that perhaps is not associated with disease progression, and in the existing literature the DNA effect, so to speak, is measurable and conventional, people who were plus/minus at conventional hybridization assay levels, which tends to be 10 to the 5th, 10 to the 6th. So, there is kind of a different disease consideration here in hepatitis B compared to HIV.

It's well documented now that many or most healthy carriers actually have appreciable levels of HBV DNA using PCR assays, and also patients who e convert and then go on to do well clinically tend to maintain low level viremia until they eventually clear s antigen, at which time many of those will lose peripheral viremia but still have DNA in the liver.

DR. HAMMER: On the DNA PCR assay, what is the

range of responses, just approximately? Is it across the population? Is there a 3 log difference in patient responses or is it much tighter?

DR. BROWN: Yes. We've seen in two different studies, our median response tends to be around 3 to 4 logs.

DR. HAMMER: And the lowest?

DR. BROWN: Sorry?

DR. HAMMER: I'm just asking what the range of response is to try to get some handle on whether there are other predictors of response rates.

DR. BROWN: Well, as Dr. Hollinger alluded to, the conventional assay has a threshold around a million, 5 million genomes per ml. Most of our patients go below that. So, the range we're seeing tends to be on the order of 10 to the 3 to -- the range of response tends to be down from wherever they started, which is typically 10 to the 7th, 10 to the 8th or above. Typically patients are going down to 10 to the 3 to 10 to the 5 range.

DR. HAMMER: Just one last question. In the briefing book, there is a multivariate modeling predicting outcome and lamivudine treatment was the key issue there. But have you looked at both baseline factors and early response factors -- you may have and I may have missed it -- as predictors of response? Because otherwise, it

doesn't really -- we have no reason to predict who are the 50 percent responders.

DR. BROWN: Right. We've looked at baseline factors quite extensively, and time permitting, we could get into that perhaps this afternoon on an individual issue basis. We've not looked at early response factors, but that's certainly something that's worth looking at as we accumulate more and more data. And we are starting to use some of the newer assays in our program as well to give us some of that sensitivity in the lower range.

DR. HAMMER: Thank you very much. We appreciate your indulgence with us and our questions.

We're running a little bit behind. We'll take a 15-minute break and reconvene at 11:00.

(Recess.)

DR. HAMMER: We're going to continue now with the FDA presentation. I believe it's going to be headed by Dr. Styrt.

DR. STYRT: I'm Barbara Styrt. I'm the clinical reviewer for this new drug application and I'd like to briefly introduce the FDA presentation for NDA 21-003 and 004, lamivudine for treatment of chronic hepatitis B.

As you're aware, the applicant has submitted results from four principal phase III controlled studies

using a 100 milligram per day dose of lamivudine for 52 weeks. In this presentation we will refer to the U.S. study, a placebo-controlled study with a 16-week post-treatment follow-up period; the Asian study, a placebo-controlled study using two doses of lamivudine with no post-treatment follow-up incorporated into the study; the interferon nonresponders study, which compared lamivudine monotherapy for 52 or 68 weeks against placebo and an active control combination lamivudine/interferon therapy arm with a 16-week post-treatment period after the 52-week treatment course; and the active control study, which compared lamivudine against either interferon monotherapy or combination therapy with no placebo control and had a 12-week post-treatment follow-up period.

The major emphasis of the FDA presentation will be on selected aspects of the data for which additional discussion may be useful. The analysis will focus on the three placebo-controlled studies of lamivudine 100 milligrams per day and on the two principal, protocol-predefined week 52 endpoints, histologic response defined as an improvement of at least 2 points on the Knodell score and e antigen seroconversion, a three-component composite endpoint defined as loss of hepatitis B e antigen, gain of e antibody, and fall in HBV DNA to below the limit of the research solution hybridization assay employed in these

studies.

We will compare the week 52 end-of-treatment results against off-treatment, end-of-follow-up results and discuss the impact of missing values on the analysis.

There will be a brief discussion of results from the interferon and combination therapy comparisons.

The three components of the composite seroconversion endpoint will be examined briefly, with additional exploratory analyses of the HBV DNA component of this endpoint.

We will also summarize some exploratory analyses of the occurrence treatment-emergent viral mutants and outcomes that may be associated with these mutants.

We will begin by presenting the FDA efficacy analysis, followed by a summary of key efficacy points, then a presentation of safety data and a summary of key safety points, and finally a brief listing of some unresolved issues which arise in review of these data and warrant further discussion.

Dr. Greg Soon will now present the FDA efficacy analysis.

DR. SOON: Thanks, Dr. Styrt.

I'm Greg Soon, statistical reviewer for this NDA.

This is an overview of my talk. First, I will

summarize the efficacy results for the histologic outcome and the seroconversion status for lamivudine and placebo treated subjects at week 52. Further, I will discuss the relationship of these two measures. Then I will discuss how treatment effects change from end of treatment to end of follow-up. Finally, I will show the proportion of subjects who met the seroconversion criteria at each visit, as well as the components of this composite endpoint with special emphasis on HBV DNA.

Now, I will first briefly review the efficacy results for histologic improvement at week 52. Subjects with a missing baseline Knodell score have been excluded.

This table shows the histologic improvement rates for the three placebo-controlled studies which includes the U.S. study, NUCA3010; the interferon nonresponder study, which is NUCB3011; and the Asian study, which is NUCB3009. The rows of this table contain the histologic outcome. "Yes" means the subjects had a 2 or more point improvement in total Knodell score, and "no" means that they did not have such improvement. Missing means the week 52 Knodell score was not available.

The numbers presented in the body of the table are the percentages of subjects in each treatment arm with various histologic responses. For example, in the U.S. study for the lamivudine arm, histologic improvement

occurred in 55 percent of the subjects, and 27 percent did not have such improvement. 18 percent were missing.

This can be contrasted with the placebo arm for the U.S. study in which 25 percent had histologic improvement. The test of difference of percent improved is statistically significant. The comparison for the other two studies are virtually identical.

Note that a minimum of 8 percent to a maximum of 20 percent of the histologic evaluations are missing and have been treated as failures. Even in the presence of this amount of missing data, it is clear that the lamivudine group has a better response rate than placebo.

Next we turn to the seroconversion. Seroconversion is defined as loss of e antigen, gain of e antibody, and HBV DNA below assay limit. A subject has seroconversion status at a visit only if a subject met all the three criteria at that visit.

We have chosen not to impute for missing e antigen and e antibody using techniques such as last observation carried forward. In our review of the data, we were somewhat surprised that the e antigen and the e antibody were not predictably durable. In these studies, for subjects, whoever had a negative e antigen, 37 percent had at least on e positive value later. For subjects, whoever had a positive e antibody, 39 percent had at least

one subsequent negative value.

In our primary analysis, the missing values have been treated as a separate category in our tables which implicitly treats missing observations as failures. This is consistent with the approach we have adopted for presentation to this committee.

This table displays week 52 seroconversion status. The sample size you see here will be slightly different than the previous slide on histology because this analysis is restricted to subjects who had a positive e antigen and a positive HBV DNA at baseline.

The first row shows the percent of subjects who met all the seroconversion criteria at week 52 for each treatment arm in the study. For the U.S. study, the lamivudine rate is 17 percent versus 6 percent for placebo. This comparison just passes the .05 level of significance, but obviously this statistical evaluation is highly dependent on how the missing data are treated in the analysis.

For the interferon nonresponder study, the response rates were nearly identical for the lamivudine treated and the placebo treated subjects.

The Asian study showed a significant difference and the amount of missing data is much lower.

Overall, we see much less statistical

consistency than was seen for histology. One study is sensitive to the missing data. One was clearly negative and the one was clearly positive.

On the next two tables, I will show the relationship between seroconversion status and the histologic outcome. These analyses were conducted to see if the seroconversion endpoint is a reliable indicator of the biopsy outcome.

This slide shows the lamivudine treated subjects in the U.S. study. My next slide will show the results for the placebo arm. This is a cross tabulation of seroconversion status by histologic improvement. The table shows number of subjects instead of percent of subjects.

If you look at the upper left corner of the table, you can see that most of the subjects who have seroconversion status equal to yes at week 52 also had histologic improvement. That's 9 versus 1.

On the other hand, for those who did not meet the three seroconversion criteria at week 52, 21 showed histologic improvement while 16 did not.

Other studies showed similar results which suggests that the ability of seroconversion status to indicate the histologic outcome is limited.

These are the results for the placebo arm. We can see that there are too few seroconverters to permit a

comparison with the results for lamivudine.

Now we turn to the second part of my talk which will compare the end of treatment at week 52 with the end of follow-up at week 68. Because we have no histologic evaluation at week 68, this analysis uses the seroconversion status only.

This table presents the number of subjects for the lamivudine group in the U.S. study. The placebo group will be shown on the next slide. Recall that treatment was discontinued at week 52.

Of the subjects who met the three seroconversion criteria at week 52, 8 also met the criteria at week 68 and 3 no longer met the criteria.

Of the subjects who did not meet the three criteria at week 52, 3 met the criteria at week 68 and 38 did not.

It is interesting to note that exactly the same number of subjects meet the criteria both week 52 and week 68, but this is because the gains and the losses are in exact balance.

For placebo treated subjects, no subjects lost the seroconversion status and 2 subjects gained status from week 52 to week 68. However, a few placebo treated subjects lost the seroconversion status in the only other placebo-controlled study with the follow-up data. There

were really too few subjects to comment on the durability of seroconversion status for placebo subjects.

Comparison of lamivudine and placebo at week 52 and week 68 will be presented later graphically, as well as all other time points measured. These tables have shown that the proportions over time reflect the gains and the losses.

In the remainder of my presentation, I will show how the seroconversion status and its components change over the course of the trial.

This is an exploratory analysis using subjects with complete data at a given time point. This differs from the primary analysis in which missing data were listed separately. We have done this to avoid having the graphs decrease over time due to an increasing amount of missing data. However, the graphs with missing values, included as failures, showed the same patterns. We have analyzed the subjects based on their randomized treatment assignment. We have also only included subjects with detectable baseline e antigen and HBV DNA.

This is the U.S. study. In this graph and future graphs, a solid line represents active treatment and the dashed line represents either placebo or no treatment. The white dashed line represents the placebo arm. The orange is lamivudine 100 milligrams. Note that the orange

line changes from solid to dashed at week 52, showing that these subjects received no treatment at week 52.

This is the proportion of subjects who met all three seroconversion criteria. This is shown for each time point. The sample size decreases over time due to dropouts. For example, 16 percent were missing at week 52 for post-treatment arms. From the plot, we can see that over the course of the study, the proportion of subjects who met all three seroconversion criteria increased in both the lamivudine and placebo groups. Recall that the statistical comparison at week 52 was not robust. In fact, the difference varies before and after week 52. This reflects changes brought about by a small number of subjects.

This is the first in a series of three slides for the interferon nonresponder study. This slide compares the two lamivudine arms to investigate the question of continued therapy versus 52 weeks of therapy. We will see that this study does not provide convincing evidence that therapy beyond 1 year provides additional benefits.

The next two slides will compare the lamivudine arms to placebo and then with the combination of lamivudine and interferon.

Subjects in the two arms shown here received identical treatment through week 52. The group shown in

yellow was assigned to receive lamivudine through week 68. The orange line represents subjects assigned to receive lamivudine for 52 weeks followed by placebo.

It can be seen that these two treatment groups diverge before discontinuation of treatment. Since these subjects had received identical treatment before week 52, the divergence is simply due to chance, and the difference at week 68 maybe are not effects of the preexisting difference at week 52. As such this study may not provide conclusive support for longer-term treatment.

Now let's add the placebo arm to this graph. Placebo is the white line. Again, the seroconversion rate goes up during the course of study. You can see that the two lamivudine arms are not clearly separated from the placebo arm.

Now let's add the interferon and the lamivudine combination arm. The green line represents the combination arm with active treatment discontinued at week 24. These subjects received lamivudine in the first 24 weeks and interferon from week 8 to week 24. It is clear that the combination arm is numerically but not significantly worse than placebo at week 52.

In summary, this trial does not allow us to distinguish between lamivudine and placebo between 52 and 68 weeks of lamivudine, nor the contribution of combination

therapy with respect to seroconversion.

This is the active control study. Orange represents lamivudine, blue is interferon monotherapy, and the green is combination therapy.

At week 52 the combination arm is numerically superior to the two monotherapy arms, but this did not achieve statistical significance after adjusting for multiple comparisons. Note also that the week 52 results appear somewhat atypical of the pattern seen over the course of the trial. The two monotherapies, represented by orange and blue, had similar response rates. With sample sizes of 64 and 80 subjects, the resulting confidence interval for the difference of response rates between the two monotherapies at week 52 had upper and lower bounds nearly as great as the response rates, suggesting that we do not have enough data to rule out a difference favoring either treatment.

The other placebo-controlled study is the Asian study. Three points are shown here because e antibody was available only for weeks 24 and 52. Again, the orange line is lamivudine 100 milligram and the white is placebo. The pink line with hollow circles is lamivudine 25 milligram. Similar to what we have seen in the previous slides, the proportion of subjects meeting the seroconversion criteria at each visit increased over time for all three arms. By

week 52, there is a difference in the proportion of subjects meeting seroconversion criteria between lamivudine 100 milligrams and placebo, and it is statistically significant, as we mentioned at the beginning of the talk, but no difference was established between the two lamivudine doses.

Now, we will change gears a little bit and examine how seroconversion is driven by its component measures, which include e antigen, e antibody, and HBV DNA.

These are the results for the U.S. study. The bottom white line represents the composite endpoint. This is the proportion of subjects who met all three criteria at each time point. The orange line represents the proportion of subjects who were e antigen negative. The green is the proportion with e antibody positive, the yellow is the proportion of HBV DNA below assay limit.

From the plot, we see that among the three components, e antigen and e antibody are very similar to the composite, but the HBV DNA component is different. While seroconversion rates and the rates of e antigen negative and e antibody positive increase over the course of the trial, the proportion of subjects with HBV DNA below assay limit increased initially and then seemed to decrease even during the active treatment.

For this reason, we will single out the HBV DNA

component for further analyses. These analyses will be presented in the following slides.

This is the U.S. study. Orange is lamivudine and the white is placebo. The lamivudine line was shown on a previous slide. As I mentioned previously, there was an initial rapid rise in the proportion of subjects with HBV DNA below assay limit. After that, there is a continual decrease, and this decrease began well before the end of active treatment.

In the placebo group, the proportion of HBV DNA below assay limit rises gradually over time. This graph raises the possibility that there may be a loss of relative efficacy well before the discontinuation of treatment.

This is the interferon nonresponder study. Yellow is lamivudine for 68 weeks. Orange is lamivudine for 52 weeks, and the white is placebo. Again, the lamivudine arms peak at week 24 or before that and then decline steadily. This relationship is consistent with the findings in the U.S. study.

Now, let's add the interferon and the lamivudine combination arm. The green line represents combination therapy. For this treatment, the proportion of HBV DNA below assay limit increases while on treatment, but once the active treatment is stopped, the proportion declines rapidly and it then follows the path of the

placebo arm.

This is the active control study. Lamivudine is shown in orange, interferon monotherapy in blue, and the combination therapy in green. The patterns we see here for the lamivudine monotherapy and the combination therapy are similar to the other studies; that is, for the lamivudine group, the proportion of HBV DNA below assay limit peaks before week 24 and then declines even when the subjects were on active treatment, while for the combination arm, the response rate rises during treatment but drops off rapidly after stopping the active treatment.

Subjects in interferon monotherapy received placebo for 8 weeks, followed by 16 weeks of placebo and interferon therapy, and are then followed by no treatment. The response rate increased between weeks 8 and 24 during active treatment, then stays relatively stable after discontinuation of treatment.

The last study is the Asian study. This study appears to be different from the other studies. Again, the orange is lamivudine and the white is placebo. The additional pink line with hollow circles is lamivudine 25 milligram. Contrary to the patterns we have seen earlier, the proportion of HBV DNA below assay limit does not decline after its initial rise. Rather, the proportion of HBV DNA below assay limit for both the 100 milligram dose

and the 25 milligram dose peak around week 8 with no apparent subsequent decline.

The placebo group is similar in pattern to the other studies.

Now I'll return the podium to Dr. Styrt.

DR. STYRT: I'd like to recapitulate a few of the points from Dr. Soon's presentation that may be important in the consideration of this NDA.

The end-of-treatment histologic response to 52 weeks of lamivudine was superior to placebo in all three placebo-controlled studies with a significant treatment effect that was consistent across studies.

Results of the principal seroconversion comparison varied in the different studies and over time within studies. There was one study, the Asian study, with a statistically significant difference between lamivudine and placebo groups, one study, the interferon nonresponder study, with no apparent difference between lamivudine and placebo in the principal predefined seroconversion endpoint, and one study, the U.S. study, in which statistical significance was sensitive to the treatment of missing values, but overall results appeared similar to the Asian study.

We were fortunate in having three placebo-controlled studies with consistent histologic results, as

it would have been far more difficult to draw conclusions from the seroconversion data alone or from the active control data.

The comparison of end-of-follow-up against end-of-treatment seroconversion status was inconclusive. It was not possible to determine whether there was a reliably persistent treatment effect after stopping therapy, but it could not be demonstrated that there was no persistence.

In addition, subjects moved in and out of the groups meeting the seroconversion criteria and each of its component criteria during therapy and after therapy.

There were also some inconsistencies in components of the predefined serologic endpoint. For example, there was a marked treatment-related discrepancy, as you have heard, between prospectively defined three-component seroconversion and its e antigen component in one of the studies, and this illustrates the potential need for more study of the interrelationships between different markers and endpoints used in hepatitis B studies.

Seroconversions did occur in placebo recipients. The frequency of these responses was consistent with reports of spontaneous e antigen seroconversion in the literature, but was sufficiently different in different studies to have an impact on the interpretation of treatment effect for the active drug.

In the studies with interferon containing comparator arms, no evident advantage was seen for combination therapy. The active control study did not show any substantial difference between lamivudine and interferon monotherapies, but did not have the power to rule out the possibility of clinically meaningful differences in favor of either arm.

In addition, it was not possible from the results of this study to confirm whether the timing of treatment and of principal evaluations on treatment for lamivudine monotherapy and after 6 months off-treatment for interferon represents the most appropriate study design for comparison of these therapies.

When we looked at subjects with HBV DNA below the assay limit at each time point, a very high proportion of lamivudine recipients in all studies achieved levels below the assay limit early in therapy. However, this striking early rise was followed by a decline in the proportion of subjects with HBV DNA below the assay limit. This decline began before the end of therapy, such that about one-third of subjects with this early response were again HBV DNA assay positive on therapy at week 52. It's not clear whether this pattern could be better defined with different assays given the many differences between the HBV DNA assays in current use, but within the measurements

employed in these studies, there appeared to be a response which was partially reversed during the treatment period.

It was very difficult to draw conclusions about the optimal duration of lamivudine therapy, and many of the points I've already mentioned contributed to this difficulty. For example, the changes over time in placebo recipients complicate any assessment of the value of successive increments of treatment. The meaning of different histologic assessment systems can be debated and the number of time points examined histologically is necessarily small. The number of seroconverters in these studies was too small to permit conclusions about loss or persistence of seroconversion-defined treatment effects after stopping therapy. The number of seroconversions during extended therapy was also too small for confident interpretation.

You have seen the graphical representation of the difference between 68-week and 52-week lamivudine groups at week 68 in the interferon nonresponder study which appeared very much like the difference between the same groups at or before week 52 when their treatment was identical.

We have also performed preliminary analyses of data from study NUCB3018, the follow-on study from the Asian study. Of the subjects in that study who received

lamivudine 100 milligrams per day for the first year and were assigned to continue for a second year, we are not able to identify a net increase in seroconversions of more than a few percentage points in the second year and cannot clearly differentiate this effect for what might occur without treatment.

Whether during or after treatment, the persistence of treatment-related changes in the components of the seroconversion endpoint was less than might have been expected, although early results from one of the follow-on studies suggests that seroconversions or e antigen loss lasting at least a few months may prove to be more predictive of long-term persistence. A single negative e antigen, positive e antibody, or even three-component seroconversion at one time point did not necessarily indicate that no reversion would occur.

For the HBV DNA component of the seroconversion endpoint, the subgroup of subjects with a fall below the assay limit followed by reemergence of DNA before the end of treatment was large enough to raise concerns about whether part of the study population is experiencing an early response and then losing treatment effect despite continuation of the drug.

Overall, the issues arising from the efficacy analysis suggest that there are still challenges to be met

in defining the best predictor of either short-term or long-term clinical benefit in chronic hepatitis B and defining the best treatment regimens to produce this benefit.

In the safety presentation, I'm going to start by discussing some exploratory analyses of outcomes in subjects who experienced reemergence of HBV DNA and/or development of viral mutations during lamivudine therapy. We considered these events to represent a combination of safety and efficacy issues, as the risk/benefit calculations for long-term therapy may be substantially altered in any patient subgroups having diminished benefit from treatment while remaining at risk for toxicity.

I will then outline some of the questions that have arisen about exacerbations of liver dysfunction as treatment-relate events in studies of lamivudine and other clinical and laboratory adverse events in the clinical trials.

Finally, I will mention some potential concerns with use of the drug in special populations which again may be considered as combined safety/efficacy issues.

Starting with HBV DNA reappearance during therapy, we wanted to see what the available data could tell us about the disease status of subjects who apparently responded to treatment and then became DNA positive again.

For this purpose, we performed exploratory analyses of subjects in all four studies who received lamivudine 100 milligrams per day for at least 52 weeks and had at least one HBV DNA below the assay limit for the solution hybridization assay before week 24, which we will call early suppression.

We divided these subjects into two groups defined as follows. Subjects with reappearance of HBV DNA on therapy experienced early suppression, but were HBV DNA positive again at week 52. Persistently suppressed subjects experienced early suppression and were also below the assay limit at week 52. We used the combined results from all placebo subjects as an additional comparator.

This slide shows a brief summary of the analyses of week 52 endpoints for these groups. The numbers are tabulated in your background package. Subjects with HBV DNA reappearance on therapy had a higher proportion of histologic responders than placebo subjects but some of them may have been exposed to recrudescent virus for only a short time.

Subjects with HBV DNA reappearance on therapy appeared to have a magnitude of change in the Knodell score intermediate between persistently suppressed subjects and placebo subjects.

Subjects with HBV DNA reappearance were less

likely to have negative e antigen, positive e antibody, or normal ALT at week 52 than persistently suppressed subjects and looked rather more like the placebo recipients for these endpoints.

HBV DNA reappearance on therapy was more common in subjects with viral mutations which have been associated with reduced viral susceptibility to lamivudine. However, this correspondence was not absolute as there were also some subjects with HBV DNA reappearance who did not have these mutations detected and some persistently suppressed subjects who did have such mutations. It was possible to define genotypes for many of the persistently suppressed subjects as mutations were sought using a PCR based assay while HBV DNA suppression was defined here by the solution hybridization assay.

We also looked more closely at groups of subjects defined by analyses of viral genotype at week 52. Mutations in the YMDD region of the viral genome associated with reduced in vitro lamivudine susceptibility have been seen, as you have heard, in some subjects with viral breakthrough during lamivudine therapy, and PCR based assays for these mutations were performed for a substantial proportion of the subjects in the four principal phase III trials at 52 weeks and for smaller numbers of subjects at selected earlier time points.

YMDD mutations were not seen in specimens from placebo subjects in these trials, were infrequent at 24 weeks of lamivudine therapy, and increased in frequency between weeks 24 and 52, and again between week 52 and week 104 in the limited data from NUCB3018.

When YMDD mutations were detected, specimens might be reported as either mixed or fully mutant, and these categories will be combined when we refer to any mutant in the following table.

This table shows the occurrence of YMDD mutations by 52 weeks for subjects receiving lamivudine 100 milligrams per day in each of the four principal phase III trials expressed as a percentage of all specimens that were reported with a genotype result or a result of no PCR amplifiable DNA. The bottom row of the table shows the percentage of mutant containing specimens that were reported as fully mutant.

Note that three of the studies, the U.S. study, the interferon nonresponders study, and the active control study, had about 30 percent of specimens reported as containing mutants, ranging from 27 to 32 percent, and in each of these studies, most of the mutant-containing specimens were reported as fully mutant.

On the other hand, the Asian study had a much lower prevalence of mutations at 1 year of treatment, 16

percent, or not much more than half of what was seen in the other studies. Furthermore, only one-third of the mutant-containing specimens in this study were reported as fully mutant. You'll recall that this was the study which did not show a progressive decline in proportion of subjects with HBV DNA below the assay limit during treatment.

However, in the subset of these subjects who were assigned to continue 100 milligrams of lamivudine for a second year in study NUCB3018 and had repeat genotype determinations at week 104, mutants were detected in 42 percent of week 104 specimens with results available and most of those were reported as fully mutant.

This slide shows brief conclusions from the exploratory analysis of outcomes according to genotype at the end of a year of therapy. Again, the numbers are in your background package and the results are similar to those for subjects with HBV DNA reemergence, some but not all of whom are the same subjects.

Subjects with fully mutant virus had a higher proportion of histologic responders than placebo subjects, but knowing that most of these viral mutations appear to emerge late in the year of therapy, we don't know how long the liver had been exposed to them at the time of biopsy.

Subjects with fully mutant virus tended to have magnitude of Knodell score changes intermediate between

placebo recipients and lamivudine subjects with non-mutant virus.

They were less likely to have negative e antigen, positive e antibody, HBV DNA below the solution hybridization assay limit or normal ALT at 1 year than lamivudine treated subjects with wild-type virus and appeared more similar to placebo subjects on these outcomes. All subject categories, including placebo subjects, tended to have HBV DNA and ALT at 1 year that were below their individual baselines.

Subjects with mixed viral populations were few in number and results were somewhat erratic, but generally they showed results intermediate between lamivudine recipients with wild-type virus and subjects with fully mutant virus.

What happens if treatment is stopped in the presence of viral mutants? There were even smaller numbers of subjects to look at here. And these are not so much conclusions as suggestions that more information may be needed.

Subjects with fully mutant virus did not have much change in ALT and HBV DNA levels after stopping treatment. They looked much like the placebo subjects and had less suggestion of rebound than lamivudine treated subjects with wild-type virus.

Subjects with mixed mutants did have post-treatment rises in ALT and HBV DNA, but the magnitude was difficult to compare with other groups due to the small number of subjects.

In the very few subjects with mixed or fully mutant virus at 1 year and repeat genotypes available after 4 months off therapy, reemergence of wild-type was detected in most but not all, and most of these still had some detectable mutants often as mixed genotypes. About one-quarter of the subjects with fully mutant genotypes at week 52 were also reported fully mutant at week 68 in the data available from the time points.

Results from the subjects with HBV DNA reappearance and/or reemergence of YMDD mutations on therapy raised some questions about whether there may be patient groups who have diminished treatment benefit over time. We could not be absolutely sure that these subjects were better off at week 52 than if they had received placebo for a year and were much less able to draw conclusions about whether they were better off continuing lamivudine than if they had stopped at the time of HBV DNA reemergence or detection of mutations.

More information is needed to define the risks and benefits of treatment continuation in such patients. Ideally it would be desirable to be able to define groups

of patients who would benefit from very long-term therapy, patients who have achieved definitive benefit, for example, whether most subjects with short-term durable seroconversion will show clinical stability off treatment over the long term, and patients who should consider stopping treatment because they may no longer be benefiting but remain at risk for adverse events if treatment is continued. And from the data so far, there may be a need to demonstrate whether some patients with HBV DNA reemergence or YMDD mutations fall into such a category.

Moving on to some of the hepatic adverse events that have been reported in lamivudine clinical trials. In the controlled trials with post-treatment follow-up, a substantial minority of subjects had transaminase flares after stopping lamivudine, which have been described to you by the applicant. Most such flares reportedly did not lead to clinical problems, and there is insufficient information to predict the results if patients are retreated.

In open-label studies that often enrolled much sicker patients, there have been occasional reports of clinically significant hepatic decompensation reported by the investigators to be potentially related to drug withdrawal, including a few with fatal outcomes.

Hepatitis flares associated with seroconversion have previously been reported in patients with chronic

hepatitis B, and in active control study NUCB3010, the applicant's analysis reports four cases in which liver function test elevations were reported as serious adverse events and were associated with seroconversion in the lamivudine arm.

We previously noted that subjects with YMDD mutations tended to have week 52 ALTs than lamivudine treated subjects with wild-type virus. In the various study reports so far, we have seen four reports of deaths in subjects with YMDD mutant virus. Two of those were in patients who received lamivudine as immunocompromised transplant recipients in compassionate use settings. The others in two other studies outside of the four principal phase III trials.

In all of these reports, the ability to interpret causality is limited by the fact that we're seeing deterioration of liver function that could be related to the patient's underlying disease and there is not adequate information to delineate the extent to which lamivudine use or cessation could contribute to such outcomes.

As you're probably all well aware, lamivudine has had extensive use in the treatment of HIV infected patients, and the current label carries warnings or precautions concerning the possibilities of lactic acidosis

and hepatic steatosis, pancreatitis, and post-treatment hepatitis flares. Laboratory values from clinical trials in HIV described in the label show modest increases in reports of neutropenia, liver function test, and amylase elevations in lamivudine-containing treatment arms. However, the clinical adverse event profile has not shown major differences between placebo and lamivudine recipients in most of these HIV treatment studies.

In the four principal phase III trials in chronic hepatitis B, lamivudine subjects had more grade 3 and 4 elevations in CPK and lipase than placebo subjects in each study for which this comparison could be made. That is, each of the three placebo-controlled studies had some increase in grade 3 and 4 CPK elevations and the two placebo-controlled studies that measured lipase had an increase from 7 percent in the placebo arm to 10 percent in the lamivudine arm in lipase values greater than 2.5 times the upper limit of normal.

The clinical significance of these laboratory variations is unclear and the subjects have not been reported as having major clinical manifestations. But these laboratory values may signal a need to be alert for possible muscle or pancreatic events with more widespread use of the drug in more heterogeneous populations.

The adverse events profiles in these trials

have also been presented to you in greater detail by the applicant, and no common new adverse events have been evident in hepatitis trials relative to experience with lamivudine in HIV therapy.

In the trials with interferon treatment arms, adverse events appeared compatible with those previously identified in trials of interferon.

There are several special populations in which more information may be needed about lamivudine for chronic hepatitis B. In patients with decompensated liver disease, it's very difficult to derive information about drug-specific events when the underlying risk of adverse events is high, but there is no suitable comparator to determine which events could be associated with therapy.

In HIV/HBV dually infected patients, there is very limited adverse event information from retrospective analysis of subjects in HIV trials who had serologic evidence of concurrent hepatitis B virus infection, and some excessive neutropenia has been reported in lamivudine-containing treatment arms, as well as shifts to ALT levels higher than the subject's baseline.

There is also the potential concern of whether some dually infected subjects might be started on lamivudine for chronic hepatitis B and inadvertently have drug-resistant HIV selected out.

In children there is very little information on lamivudine in chronic hepatitis B with a safety database of about 50 subjects treated for 4 weeks at varying doses, HBV DNA measurements using a different assay from the principal adult studies, and no opportunity to derive information on the relative potential for completeness and rapidity of viral suppression, seroconversion or histologic outcomes, emergence of viral mutations, or long-term toxicity.

To summarize the major safety points that have arisen in consideration of these data, the reemergence of HBV DNA and/or emergence of YMDD mutations appear to have potential associations in these exploratory analyses with outcomes suggesting diminished treatment benefit. The potential for exacerbations of liver dysfunction, either during therapy or in association with stopping therapy, is a concern, and more information would be desirable on the risks in different patient groups.

In summary, we have three different studies in support of the safety and efficacy of lamivudine for chronic hepatitis B with a very consistent effect on the primary histologic outcome and more variable indicators of beneficial effect on seroconversion outcomes. As a preliminary to further discussions, we'll note that the information in this NDA raises some interesting and unresolved issues.

For evaluating efficacy, designing future trials, and monitoring individual patients, it would be desirable to have more definitive information about the best markers for predicting short or long-term benefit in chronic hepatitis B. How frequently changes over time in this disease are due to drug therapy as compared to events that would occur spontaneously and how durable the drug-induced changes will be either on or off therapy remains a challenge to determine even in controlled trial settings.

While uncontrolled data are even more difficult to interpret, at this stage of development, it's often unclear what is the best comparison group for evaluating a new treatment and the best trial design for making these comparisons. A major issue in future trial design may be how best to evaluate the potential for combination therapies.

Among the unresolved safety issues, more information on patterns of liver dysfunction and hepatitis flares associated with either use or cessation of lamivudine would be of particular interest and information on the effect of retreatment in patients who have rebound or relapse after stopping drug could be important to many treatment decisions.

In addition, very long-term effects of this drug in chronic hepatitis B are, of course, yet unknown.

There are several potential patient populations for whom more information could result in altered assessments of the risk/benefit balance of various treatment strategies. These include patients with decompensated liver disease, pediatric patients for whom safety and efficacy have not been demonstrated, and treated patients who seroconvert -- should they stop therapy while they have a durable response -- or who develop viral reemergence and/or resistance related mutations. Can we predict who is most at risk for such events, and should some of these patients stop therapy because its benefit is diminishing or lost?

Overall, the studies presented here show some encouraging results but also illustrate how much more it would be useful to know about selection of treatments, selection of patients for treatment, timing and duration of lamivudine therapy for hepatitis B.

Thank you.

DR. HAMMER: Thank you very much.

I'm going to ask that we defer questions for the FDA presentation until after lunch and move to the open public hearing because some of the individuals who have signed up have afternoon commitments. So, we will move to the open public hearing. I would ask that the people who come to the microphone, identify themselves, speak for no more than 4 to 5 minutes, and announce any financial

disclosures that are relevant.

The first individual is Scott Lincoln.

MR. LINCOLN: As the Chairman said, my name is Scott Lincoln, and I would like to inform the committee that the expense to fly me here to Washington from San Francisco has been covered by Glaxo Wellcome.

I would also like to say thank you to the committee for allowing me to speak about my health experience and how my health has improved since I started taking the drug lamivudine.

I also wanted to put a face and a name to hepatitis B.

I was diagnosed with hepatitis B in December of 1991 at the age of 28. I became quite ill from the start. Within a month, I began to experience excruciating pain in my legs. As the months progressed, my health continued to decline. By May of 1992, I was taking 30 milligrams of valium because the pain had increased so in my legs. The pain was so intense that I slept about a couple of hours each day. Suicide seemed to be my only escape from pain, and I came very close to ending my life.

By June I was begging my doctor to see a neurologist. After seeing the neurologist and having two biopsies taken from my calves, consisting of nerve, vessels, tissue, I was diagnosed with polyarteritis nodosa,

a vascular disease brought on by the hepatitis B. The sedimentation of my blood was at 153 when normal is 13. The polyarteritis nodosa, PAN for short, was ravaging my organs and my joints.

August and September of 1992, my health continued to decline. I was on massive doses of steroids and spent many hours in the emergency room due to uncontrollable vomiting.

By the middle of September, my doctors had realized that the PAN had killed my gallbladder and I had emergency surgery to remove it. My parents arrived from the Midwest while I was still in surgery.

6 days later my bowel perforated which caused peritonitis. Once again, surgery was performed and my bowel was repaired. Other complications had arisen and my condition was serious by this time.

I was then given my first dose of Cytoxan, a chemotherapy drug, to suppress my immune system since it was trying to kill me. 10 days later my bowel perforated three more times.

My mother was told to call the rest of the family since they did not expect me to live. This time they removed a little over a foot of my bowel. I never thought I would leave the hospital alive.

The next 3 weeks I was given more Cytoxan and

was still taking high doses of steroids. Finally, this treatment seemed to be working. My prognosis was not good, but my faith and determination were strong. I was released from the hospital on November 8th, 1992 and was being cared for at home by my mother. I weighed 98 pounds and no longer could walk.

I continued to receive monthly injections of Cytoxan for 1 year. The treatment made me very ill and there were many times I wondered if it was worth it all. I had lost my career. I had to file bankruptcy, and I now lived on Social Security. I was still determined to survive and I started walking with assistance and continued to improve slowly as the years went by.

By October of 1995, I was experiencing severe pains in my right side. This is when it was determined that the hepatitis B was now chronic and my liver was failing. By January of 1996, the hepatitis B was replicating so fast that my case was transferred to the University of California at San Francisco to be placed on the liver transplant list. I was in the end stages of liver disease.

At the same time, I had been screened and approved to enter a study with a drug called lamivudine. On February 6th, 1996, I started taking 100 milligrams of lamivudine. Within 2 weeks I had started to notice an

improvement in my health, and those improvements were I wasn't confused. I could eat. The fatigue was considerably less. By the end of the first year on lamivudine, my liver enzymes were back to normal and my health had dramatically improved. After 6 years, I reentered the work force in August of 1997.

Being here today and knowing this drug can save lives gives meaning to the hell that I went through. Please approve lamivudine for the use with hepatitis B so no one else will have to suffer as I have.

Thank you.

DR. HAMMER: Thank you very much.

The next speaker is Timothy Block.

DR. BLOCK: I'm Timothy Block. I'm a professor from Jefferson Medical School and the cofounder of the Hepatitis B Foundation and a member of the Delaware Valley Chapter of the American Liver Foundation.

I'd also like to thank the committee for allowing me to speak. I disclose that Glaxo Wellcome has made contributions to the Hepatitis B Foundation and has offered to pay for my travel here.

The Hepatitis B Foundation is a nonprofit organization that's dedicated to finding a cure for hepatitis B, promoting awareness about the problem of hepatitis B. When we founded the Hepatitis B Foundation in

1991, it was because of a personal story of a small boy who was infected with hepatitis B, and at that time there were no therapeutic options. That child, like hundreds of millions of other children like him, faced a lifelong stigma and life with a time bomb inside him of a virus that could go off and cause consequences because, of course, nobody knows which of the 300 million hepatitis B carriers in the world will ultimately suffer the severe symptoms associated with the virus infection.

At that time we were assured by our clinicians and by others that with proper attention and resources, good therapies for the treatment of this disease were right around the corner. I decided to change my professional career and work towards promoting awareness about hepatitis B and studying it for myself.

As I mentioned, what I'd like to do now in the next couple of minutes is tell you again and put the personal faces, as the gentleman before me did, on the 300 million individuals who are chronically infected and face lifelong doubt.

Despite the availability of a safe vaccine, which is of course of no value to those who are already infected, there still remain more than 200,000 infections in this country alone annually with hepatitis B. Most of those are in the young adult population.

I'd like to say now that we're very optimistic about the future for those who are infected with hepatitis B because perhaps the predictions of the experts who counseled us 8 years ago may be coming true.

Of course, interferon alfa is the only currently approved therapy for hepatitis B, and its even limited therapeutic value gives us hope that this is a disease that can be cured. But interferon alfa is only valuable in a minority of the population of those infected with hepatitis B, and for anyone who has been involved as a caregiver or as a counselor or as an infected individual, the untoward side effects of interferon make it imperative that alternatives be found.

We believe, because we're aware of the animal data, of the human data that are coming, that perhaps lamivudine is our current best hope. It's of course just the most developmentally advanced in a whole series of so-called polymerase inhibitors. Hopefully it won't be the last of these drugs that you'll be seeing, but it's certainly the one that we're facing as giving us the most hope right now.

It's worth mentioning that the oral availability and low toxicity, relative well tolerance makes it all the more attractive and user friendly.

Of course, we'll be keeping an eye on the

ultimate efficacy of the drug and mindful of the resistant mutants that emerge and other possible drug interactions. But nevertheless, it's the medication that's giving us the most hope.

So, I hope from the human side that other effective therapies will be found and you'll be considering those soon. But right now lamivudine gives us the current best hope.

Thank you very much.

DR. HAMMER: Thank you.

Nelson Whittington?

MR. WHITTINGTON: Good afternoon. I would like to say welcome to the committee and to guests. I am from Fort Lauderdale. My name is Nelson Whittington.

And I would like to say that I initially, after some success with lamivudine, took it upon myself to contact Dr. Brown at Glaxo Wellcome to personally say thank you and offer my assistance at any time. And here I am today, and I appreciate their assistance in my transportation to come here and speak to you today.

I want to thank you for the opportunity of speaking about a subject that is near and dear to my heart and my liver. I also speak on behalf of all who are currently suffering with the disease of hepatitis and its many consequences. I consider it a great honor to share

with you an overview of my situation and how lamivudine has drastically altered my life.

You have been presented with a great deal of documentation regarding the research, the studies and facts of what I like to call a wonder drug. I am in no way a physician or doctor of pharmaceutical research, nor do I even understand how lamivudine works, but I am a person that represents one of the statistical facts that is before you.

I'm a musician whose world collided with the medical profession in December of 1993 when I was diagnosed with chronic hepatitis B. Before my diagnosis, I was a person who never got sick. I very rarely even got a cold or a sniffle, and was fortunate to still have all of my original parts, my wisdom teeth, tonsils, appendix, et cetera. Of course, at the age of 39, I was not too sure about the amount of warranty left on any of them.

I initially went to my doctor with what I now recognize as symptoms of cirrhosis, and after some testing, they determined the cause, hepatitis B, with a viral count in the millions. According to the doctors, I had contracted the disease over a decade prior and, as my health goes, never displayed any symptoms whatsoever, not even jaundice. With chronic hepatitis and 80 percent of my liver compromised, the future was not very promising.

I was told from the first that lamivudine was being researched, but I had a platelet count that was far below the hospital protocol minimum of 100,000 to be included. The final analysis was that I had about 1 year, maybe more, to enjoy life and get my affairs in order. Needless to say, I was devastated.

After getting over the initial shock, I proceeded to get a second, third, and yes, even fourth opinion. They were all the same. Several months had passed, and I remembered the name lamivudine from my original diagnosis and made phone calls all over the world trying to get the drug and at least try to do something because with chronic hepatitis no liver would ever be granted.

Obviously, I finally got FDA approval to be included on the study on a compassionate basis and the drug was in my hand by late October of 1995. Do the math. By this date, I was already on borrowed time. I began daily doses immediately, and while taking lamivudine, monitoring blood tests were set for the next 6 months to follow its progress. The first test in 4 weeks and then every 2 weeks thereafter.

4 weeks later I did take my first test and the results read negative. The second test was taken the next day to ensure a correct response, and it as also negative.

I was, as were the doctors, extremely surprised and elated.

Thinking positively, as I do, that lamivudine would be a success, I had already made tentative arrangements for transplant. Just 5 days after those test results, December 5th, 1995, I was on a plane to Northwestern Medical Center in Chicago to start the vigil for a liver.

Call it whatever you like, luck, good fortune, or a miracle, but a matching donor organ became available only a month later, and transplantation took place on Tuesday, January 8th, 1996. The following Friday, just 3 days after my surgery, I was doing so well they discharged me from the hospital. January 21st I flew home to Florida, still donning my stitches. By mid-February I was driving again and able to resume some sort of normal life.

Well, here I am today, 2 years and 9 months later, speaking to you with a blood report that would make most healthy people green with envy. To date my viral tests continue to be negative. In fact, 4 months ago, the doctors told me that my tests were actually showing signs of immunity.

As I mentioned before, I'm a musician, a singer, and conductor. Since my transplant, I have lived every day with a renewed enthusiasm in my personal as well as professional life. In the last couple of years I have

performed for approximately 100,000 people in one capacity or the other, most of it while touring the State of Florida singing as one of the three Florida tenors. I also do many other performances on my own, making time for occasional appearances for Transplant Foundation fund raising events.

However, there is no doubt in my mind that the most meaningful performances were in June of 1996, only 5 months after my transplant, when I was able to sing for the celebration of my parents' 50th wedding anniversary and also April of 1997 when I was fortunate to sing for the wedding of my youngest brother Jeff.

Singing for thousands of people, my family, and being able to complete my life and fulfill my dreams is all directly linked to medical research, a drug called lamivudine, and an anonymous organ donor, and a medical community dedicated to better health for America.

I want to conclude by thanking you again for the opportunity to speak today. At this point in my life, I feel I have received an unexpected medical education, and especially today, and deserve some kind of diploma. Well, I have my diploma and I carry it with me every day right next to my heart. It's my new liver. Words could never express the happiness I experience each day knowing that I do have a tomorrow.

Today I want to share with you my hope that

this drug, an opportunity for life, may continue into the future granting multitudes of afflicted people the same positive results that I have experienced. I really consider lamivudine to be a true gift of life.

DR. HAMMER: Thank you very much for those comments.

Alan Brownstein?

MR. BROWNSTEIN: Good afternoon. I am Alan Brownstein. I'm the President and Chief Executive Officer of the American Liver Foundation.

ALF is a national voluntary health agency dedicated to preventing, treating, and curing hepatitis and other liver diseases through research and education. We are made up of patients and families, as well as medical and scientific leaders organized through chapters throughout the United States. I wish to disclose that over the past 3 years ALF has received unrestricted educational grants from Glaxo Wellcome in support of our educational programs.

I am joined here today by Mary Gong Sweeney of Pittsford, New York and Ralph Difonzo of Douglaston, Queens. They have come down here to share their personal stories as patients who have been afflicted with chronic hepatitis B.

We are pleased that you are reviewing the new

drug application for lamivudine for the treatment of chronic hepatitis B. We are not here today, however, to speak to the safety or efficacy of lamivudine, but rather to speak to the urgency concerning chronic hepatitis B and the need for expeditious review for all therapeutic agents considered for the treatment of chronic hepatitis B.

As you know, hepatitis B is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. There are more than 1.2 million Americans with hepatitis B infection and an estimated 15 to 25 percent will die of related complications. That gets translated to 6,000 deaths per year.

According to the World Health Organization, as you heard from the previous speakers, this is an epidemic that is ravaging other parts of the world to the extent that there are more than 1 million lives taken each year.

As you also know, at this time alfa interferon is the only FDA approved therapeutic agent known to have a lasting beneficial effect in the treatment of chronic hepatitis B. This treatment has been known to produce long-term remission in only 25 to 40 percent of the patients who have taken it. Thus, there is a dire need for more treatment options for the majority of patients with chronic hepatitis B who do not respond to interferon therapy.

Without further therapy, many more will go on to die, and those who are more fortunate will receive liver transplants, as we've just heard.

We are optimistic with the development of additional antiviral therapies, one of which, lamivudine, you are reviewing here today. We are hopeful that nucleoside analogs will help a number of patients who do not respond to interferon alone. We are grateful that you are giving all your attention to this in your review here today. We are also optimistic about the future, about other approaches, immune-directed and molecular, that are in the pipeline which you'll be reviewing in the future.

In closing, we thank you again for your attention to hepatitis B and your understanding that there is a critical need for new therapeutic options.

I am now honored to read a brief statement from Mr. Edmond Blake who was unable to join us here today, and this is to the Food and Drug Administration.

"In 1973, I contracted hepatitis B which subsequently became chronic. I was treated twice with interferon. The first time succeeded in bringing down SGPT and SGOT enzyme counts, but they went back up after treatment termination. The second treatment had similar results. In subsequent years, my condition deteriorated to the point that in June 1993 the prognosis was cirrhosis,

cancer, or even early death.

"After waiting 6 months, I received a liver transplant in December 1993, about the time when I may have had a week or 2 to live. The liver transplant was highly successful, and all the tests since have shown a normal, healthy condition. However, I must receive costly hepatitis B immune globulin, HBIg, infusions every 2 months to prevent hepatitis B from attacking the new liver.

"Needless to say, if a drug is successfully developed and utilized soon to remedy chronic hepatitis B, thousands of lives may be saved with considerable financial savings from the costly procedures I went through of over $500,000. The need is great and the time is short."

That's signed from Edmond Blake of New York City.

Now I have a special honor of introducing to you Mary Sweeney and Ralph Difonzo. Mary.

MS. SWEENEY: My name is Mary Gong Sweeney and I am a chronic hepatitis B carrier. I would like to share with you how I came to learn that I have hepatitis B.

In 1985 my brother Jim was diagnosed with liver cancer. He was prompted to medical attention when he experienced shortness of breath. Being an athlete and a nonsmoker, he found this very disturbing. Further tests revealed that he had liver cancer caused by the hepatitis B

virus. 2 and a half months later, he died at the age of 36.

At this time it was recommended by the doctors that the entire family be tested, and we all tested as positive carriers as well. We were put on a testing regimen that consisted of blood tests and ultrasound every 6 months, and in spite of being tested, 2 and a half years later, my mother was also diagnosed with liver cancer. 2 and a half months later, she passed away at the age of 62.

At that time our testing regimen was changed to the blood tests and ultrasound tests done on alternate 6 months so that every 3 months one test or the other was done to track and slight changes.

My mother died feeling very guilty and responsible for having infected her family, and I'll always regret that I was not able to explain the situation to her more thoroughly.

Anyway, it was at that time that as a result of the blood tests, I began to show a pattern of fluctuating enzyme levels. I was referred to a liver specialist who recommended interferon therapy for me. It was explained up front that the chances for success were very low for someone like myself who has been a carrier for many years. The interferon therapy failed. After 2 months it was obvious that it was not having any effect, and at 3 months

I was taken off of the drug. At that time my hair started falling out, and I lived with that for 2 years before I finally gave in and had it all cut off.

At the failure of the interferon, I luckily had another option and that was antiviral therapy with lamivudine. I have been taking 150 milligrams daily for 3 or 4 months now, and presently I'm awaiting test results from some blood work. Depending on those results, I may be taken off of lamivudine.

I'm eager to have other options available to me. If the lamivudine doesn't work, I need to have other options. Without other options, I feel like I'll be up against a brick wall, and without other options, I'll be looking at my carrier status of the virus as a time bomb waiting to go off. So, I hope to not have to deal with that.

Thank you for your time.

MR. DIFONZO: Good afternoon. My name is Ralph Difonzo. I'm 63 years old.

In 1994, the early part of January, I was diagnosed to have hepatitis B, cancer, and cirrhosis. After long procedures, I was able to get on a waiting list of liver transplant. December 29th, 1994, I was blessed. I received a transplant. 6 months after that, I was able to have a normal life. It was really great. It was

wonderful.

I was receiving an infusion of HBIg every 2 months, and it was okay for about 6 months. At the end of the year, exactly December the 29th, we had a rejection. We took care of that and we went on for another 6 months.

And at the end of July 29th, 1996, I received an HBIg infusion. We used to get one every 6 weeks. The next one would be September the 15th. However, there was none available. I was left without a medicine for about 3 weeks, which at this point my liver became infected. So, we had to go through the whole procedure again. I was fortunate enough to recuperate, recover from it.

In 1997, in March, my doctor put me on one monthly infusion, every 30 days infusion, of HBIg and also 450 milligrams of Epivir. I had 18 months. It was just wonderful. I'm having a normal life, and I'm the happiest man on the face of the earth.

Please approve this medication.

My concern is 4 years ago I used to take the infusion every 2 months. 2 years later I was taking it about every 6 weeks. Now we're down to a monthly infusion. What's going to happen 2 years down the road? So, we would like, if it's possible, some other options, if that's possible.

Thank you very much. Have a good afternoon.

DR. HAMMER: Thank you very much, and on behalf of the committee, I'd like to thank all of the speakers at the open public hearing for their eloquence and impassioned statements.

Before we close the open public session, no one else has signed up, but if someone does want to speak, this is the opportunity to come forward.

(No response.)

DR. HAMMER: If not, the morning session is closed. We'll reconvene at 1:30. Thank you.

(Whereupon, at 12:33 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:35 p.m.)

DR. HAMMER: Can I ask the committee members to please convene at the table so we can start?

Thank you. I'd like to convene the afternoon session for our discussion for the indication for the treatment of chronic hepatitis B.

We have some time, a few minutes, for the committee members to direct questions to the FDA presenters, in case there are any. I'm not going to specifically go around the table, as I did this morning, but will allow people to ask sporadically as the need arises. So, does anyone have questions specifically for the FDA presentation? Henry?

DR. MASUR: Dr. Styrt, actually I was very intrigued by a number of aspects of your analysis. But in terms of the response of the Oriental cohort as opposed to others in terms of surrogate marker, were there any predictors from baseline variables that would have suggested why that cohort had a better DNA response than the other cohorts?

DR. STYRT: Well, there certainly are a number of things that are different about the group that was enrolled in that study as a group. For example, they were not required to have as much evidence of liver inflammation

by biopsy or by ALT to be enrolled in the trial, and a small proportion of them had previous experience with interferon, although most of the were treatment-naive. And clearly there were differences in the mode of acquisition of disease and presumably could also be differences in genetics either of the host or of the virus. But in terms of other specific predictors -- the applicant may also want to comment on this -- we didn't have other specific baseline variables that seemed to predict the differences in response.

DR. HAMMER: Does the sponsor want to add anything to that?

DR. BROWN: I think the term "difference in DNA response" was used. We didn't fundamentally see that. It may have been because we looked at the data a little differently, but we did do some regression modeling of things like seroconversion, for example.

DR. MASUR: I'm sorry. You didn't see a difference in durability of response?

DR. BROWN: Correct. The FDA did look at the data a little differently than we did. We had analysis called sustained HBV DNA response, and I don't know if that's worth putting up, but in a nutshell, there was a marked difference between drug and placebo in both the Asian multi-center trial and the U.S. multi-center trial

and the other placebo-controlled study in what we analyzed as sustained DNA response. That was specifically patients with detectable DNA at baseline achieving a negative value and then maintaining negativity to the end of week 52. DNA response -- did we keep it as 2 or 1? Sustained was at least 2 and then to the end of treatment.

There were some differences across studies, but when we did some regression modeling of baseline factors for things like e loss and e conversion, ethnic origin did not come up as predictive in those kinds of analyses of predictors of sustained response. That's really the point I wanted to make.

DR. HAMMER: Please.

DR. HAMILTON: So, these are the tough questions coming up now.

Not being a hepatologist, I don't actually see that many patients with chronic hepatitis B and would defer to the comments I think of my associate on the panel, who I know is a clinician with chronic hepatitis B, and maybe others to further characterize for me and maybe for others what these people's clinical conditions are. I know we heard this morning, as Scott said, some impassioned and important testimonies as to the impact of hepatitis B on their lives. But it's my sense that hepatitis B that's chronic in the majority of individuals is not quite that

dramatic. I guess to that end, A, I'd like to hear some commentary about what a typical population of patients might be like or in fact specifically if the sponsor can give me some sense of what their clinical condition was, and how that clinical condition in some objective manner was modified by this year or so worth of therapy.

There has been an accounting of what the adverse side effects were and so on, but I guess I'm looking for something a little more global, a little more realistic that I think of when I'm talking to a patient in the clinic. You know, how are you feeling, and X, Y, and Z? I don't think of them in terms of placebo or active control study modes but as people.

So, I guess the question seems a little vague probably, but does the sponsor have some clinical data that would be of use to me in thinking in terms of how useful this drug is going to be in real terms to the patient? Because the patient, of course, doesn't give a rip if his ALT is twice normal or if his viral load is 3 logs down or anything like that. He wants to feel better. So, were there quality of life measures, for example, that would be useful in assessing this?

And there are some other kind of derivative questions, but maybe I'd start off with that one. Maybe before they respond, Blaine, maybe you could help me

understand what these patients are like.

DR. HOLLINGER: Well, I could, John, but there are a couple of people the sponsor has here who have been involved in some of these studies such as Terry Wright and Bob Perrillo and Jules Dienstag who actually have admitted these patients into these studies. Because I agree with you. I think it would be nice to know what they are.

The bottom line is like hepatitis C, many of them have no symptoms initially -- and that's one of the problems with these diseases -- until they develop really serious end-stage liver disease. But maybe they want to answer that question because they had to make a choice for that.

While they're doing that, they might also comment along this same line, if you could, about these missing values, like the biopsies. Why were these biopsies not done? Was it because they had bad disease like cirrhosis? They chose not to biopsy them, which could then bias the study? Or were there other reasons that this data was missing either for biopsies or for blood samples at the week 52?

DR. DIENSTAG: The biopsies were missing because second biopsies in clinical trials of this sort by definition are for research purposes, and many patients decline to have the second biopsy done. In some cases,

whether a patient is willing to have a second biopsy is determined largely by their experience with the first biopsy.

As far as the impact on patients, I think most patients with chronic hepatitis B, at least the ones we see in our studies of patients who have compensated disease, are pretty healthy. Some of them have chronic fatigue that limits their ability to function, but the important thing about hepatitis B is that in the presence of ongoing virus replication, the disease tends to be an ongoing one associated with liver injury. There are long-term follow-up studies in such patients, and in some studies the 5-year survival can be as little as 50 percent in patients with severe chronic hepatitis B. In those studies, the patients who are the ones with the most severe disease are the ones who have the highest level of virus replication. This is somewhat analogous to hepatitis C which is a progressive disease, but here, where replication occurs, there is ongoing liver injury and there's a very nice correlation.

It's very difficult to show an improvement in quality of life during the course of a trial of this sort. Now, if you take interferon, on the other hand, patients who come into clinical trials who feel reasonably well, feel pretty bad during therapy. And there it's even more difficult to show quality of life improvements because they

feel much worse on therapy than off. Here we're not dealing with that. Patients don't even know they're taking the drug.

I don't know if that satisfies your inquiry, but it is a progressive disease and it may not be progressive in a month or 2, but over the course of several years it can be a very devastating disease.

DR. HAMMER: Jules, please state your full name and affiliation for the transcript please.

DR. DIENSTAG: I'm Jules Dienstag. I'm a hepatologist at Massachusetts General Hospital, a clinical investigator for these trials. I guess in a sense I'm here as a consultant today.

DR. WRIGHT: I'm Teresa Wright. I'm also a hepatologist. I've also run trials with Glaxo Wellcome. I'm Chief of GI at the VA in San Francisco and Associate Professor of Medicine at UCSF.

Dr. Hamilton, it's actually rare as a clinician, as a physician, as opposed to a surgeon, to see an intervention that makes a difference. We have gone over the last 6 years from not being able to transplant patients with hepatitis B infection to the point now where they are superb candidates for liver transplantation. The only reason that we've been able to do that is the availability of nucleoside analogs. The only one we have experience

with so far is lamivudine and also with the use of high dose hepatitis B immune globulin. So, it has been an enormously gratifying experience over the last 6 years where we have been able to take people who have no option therapeutically to give them an extremely good outcome. So, that is the transplant patient.

In the chronic hepatitis B patient, I think Scott Lincoln's testimony this morning about the improvement of his PAN is actually quite unusual. That's not a group of patients that we have studied. I think most patients with chronic hepatitis B have a good quality of life. Many are asymptomatic, but we know that this virus in man is associated with death in about 50 percent of the time.

So, I think there is no doubt about the ravages this virus causes, and I just hope that this is just one of many therapies which are going to allow us to stabilize disease, reverse disease, and hopefully prevent the need for liver transplantation. So, I think there are many reasons that we as hepatologists are very encouraged by being involved in these trials. Thank you.

DR. PERRILLO: I'm Bob Perrillo and I'm head of the GI and Hepatology Section at the Ochsner Clinic.

I've dedicated the last 18 or 19 years to antiviral therapy of hepatitis B, and I've seen many of the

things that the other two physicians have just alluded to.

I'd like to point out that with the decompensated patient population, not only are they more likely to be symptomatic, but they have less viable options. They don't have a lot of time. We don't have to calculate it in 5-year survivals. It could be shorter than that.

Interferon is something I've had first-hand experience within these patients. A few years ago, we published that on a multi-center trial looking at decompensated hepatitis B. It's a very, frankly, dangerous therapy in many of these patients. It leads to immunologic activation, flaring of their ALT, and it's a real trial by fire. So, we have had another option provided to us in lamivudine. So, even going beyond quality of life indices, we now have a safer approach to managing these patients.

I think the other thing I'd like to draw comment to is that we not lose sight of the fact that in a perfect world, yes, we would have everyone appropriately vaccinated, but that simply doesn't exist. These people are infectivity reservoirs for the community and that leads to actually many of the young, predominantly male patients I see being morally devastating by the fact that they know that they're infectious for intimate contacts. So, we now have an option, a safer option than interferon for the

decompensated patients and an equally effective option in the non-decompensated population to limit this infectivity situation.

Thank you.

DR. HAMMER: Thank you.

Ms. Melpolder, did you have a question?

MS. MELPOLDER: I had an observation about the Asian population, in addition to the sustained HBV DNA data that FDA presented. It seemed that they had about half the incidence of mutation that the other studies showed. I just wondered if there was some genetic predisposition that prevented the mutation of the virus in the Asian population.

DR. HAMMER: Does anyone want to tackle that challenging question?

DR. BROWN: I think the correct term is exploratory analyses. We've done a number of exploratory analyses of these kind of data, and when we did some regression modeling, using kind of a standard set of potential baseline covariates, we did in fact find in a sense -- these have to be considered kind of post hoc or retrospective observations, if you will, that would certainly need prospective confirmation. It didi appear that the Asian versus caucasian did signal a lower incidence of YMDD variants -- if you will, in Asians versus

caucasians.

When we removed that as the first observation, the first level in the multivariate, then we did see potential impact of others, but these are oftentimes not reaching statistical significance and need to be considered exploratory. That's a fancy way I think of saying we don't know why, but we do seem to see a little bit lower incidence of the YMDD variants in the Asian population even after adjustment for some of the covariates such as all the standard kind of diseases associated covariates.

DR. HAMMER: If I could ask a corollary question. How sensitive is the assay to picking up mixtures of mutants? Your PCR assay of looking for the YMDD mutation, what proportion of mixtures can you pick up? 20 percent, 50 percent?

DR. BROWN: The overall threshold level of detection in Dr. Condreay's assay was approximately 1,000 genomes per ml. Then as I mentioned, the typing is actually done by an RFLP based assessment. So, mixed virus -- basically when the mutant is present at a 5 percent or greater level within the total population, it is detectable. And what we called mixed was anywhere between 5 and 95 percent because you can see, in a sense, both bands in the gel I guess is the colloquial way to say it, whereas at less than 5 percent mixed, of course then the

mutant becomes the fully mutant.

DR. HAMMER: Have experiments been done for individual clones to try to be more sensitive as to whether you've got mixtures or --

DR. BROWN: No. I think we can say we haven't done multiplex cloning and that sort of thing.

DR. STANLEY: Dr. Hammer, as I understood Dr. Styrt's data, though, when they analyzed it after the week 104 follow-up, there was about 42 percent resistance in the Asian population. So, it would appear to maybe just be a delay as opposed to an actual decreased level.

DR. BROWN: That's certainly possible.

DR. EL-SADR: I'm wondering. I'm going back on the dose again. Is it possible that somehow the Asian patients are smaller in size or something about the dose and you're able to sustain a higher level? The whole thing is sort of level of drug, suppression of virus, prevention of resistant mutants.

DR. BROWN: That's an excellent thought. We did put body size parameters into the multi-step regression modeling and the weight and height and body mass index were factored into it. But the Asian versus caucasian assessment came up independent of body mass index.

DR. EL-SADR: How about pharmacokinetics? Do you have some pharmacokinetic data in that population?

DR. BROWN: We do in fact. The PK data might Dr. Bye want to speak to that, but it looks remarkably similar to PK in westerners.

DR. BYE: Dr. Bye, Glaxo Wellcome.

We did a population kinetic analysis and there was no difference between the caucasian and Oriental subjects, and we also did a high powered bioequivalence type study, again there was no difference comparing against caucasians and Orientals. So, I don't think it's a PK issue.

DR. HAMMER: Dr. Sjogren.

DR. SJOGREN: I'm sitting here and wanting to rise to the challenge that Dr. Hamilton set up thinking as a hepatologist more than a researcher. I work at Walter Reed just a few blocks down the road, and I've been there since 1981. So, I've seen clinic patients with hepatitis B way before any kind of therapy was available, where we could only follow them or study the natural history and see them, indeed, get in trouble very often.

Then as interferon came along, where we've all worked with it and we are satisfied when a third of the patients respond, but then obviously the other two-thirds are out there with their hepatitis B that cannot be controlled.

In my population, a lot of the people that I

see are young, just by virtue that they're in the Army, and when you get all the older, the Army doesn't want you anymore. You got to go. So, I see a lot of these patients with active hepatitis B that don't respond to interferon.

I've never worked with Glaxo. This is not a complaint.

(Laughter.)

DR. SJOGREN: It's just stating the fact. Indeed, I was not able to secure a compassionate use protocol with them. So, I'm pretty objective I think. They don't owe me nothing. I don't owe them anything.

But my hospital has Epivir because we treat HIV patients, and so I reach out to lamivudine as a hepatologist and with great concern, but at the same time evaluating the last 2 years that it has been available to us and noticing that my patients did get better. The ALT got better. The DNA disappeared in a great proportion of them. I haven't biopsied all of them as the studies have shown, but listening to the presentations and reading their material, I observed that the liver histology has improved. So, all I know, I come away thinking this is a good drug. This is a good alternative.

I still have a lot of questions that need to be answered. I think the treatment with interferon is one of them. The long-term therapy is another one, and some

others that probably we'll discuss later this afternoon.

But I know in my young patients and in my older patients that the drug is providing a hopeful therapy in terms of reducing the DNA and, as I understand now, improving the histology. I'm disappointed that the serology is not any better, but at the same time I am understanding that the serology may not be all what we have thought it would be. They may not be the clinical parameters to follow, that we still have a lot to learn.

But like I said before, in rising to the challenge of thinking as a clinical doctor, I think lamivudine offers a definitive hope to some patients where there was nothing to be done for them in the past.

DR. HAMMER: Thank you.

Blaine?

DR. HOLLINGER: Scott, I've got some comments and some observations. This is of questions, if I could please.

The comment, first of all, I think is what Dr. Perrillo said, is we should never lose sight of the fact that, distinct from HIV, HBV does have a vaccination, and we should never lose sight of the fact that the control of this throughout the world is going to be elimination of hepatitis B. Then we don't have to worry about whether these drugs work or not and how well they work. So, we

should always push for that.

Now, having said that, on some of the FDA's work that was presented, the impression that I got in looking at the data was that the sponsors probably have not reached the optimal endpoint at week 52. Most of the data was still climbing at the end of week 52. Yet, at the same time, there seemed to be an increased development of resistance going on, and at some point these are probably going to cross. Therefore, you may have less effectiveness going on because there's more resistance being developed.

I guess the question would be -- again, it has been asked -- is whether longer treatment or higher dose are better in this case. I think you presented some data from 3018 that maybe did not show this, suggested it did not seem to be much better at 2 years. But this is a very important issue because if resistance does develop and if you can suppress viral replication early, very early, with higher doses, then you might suppress the development of resistance.

Now, I know there are some papers. For example, I think there is a paper being presented at the AASLD coming up which suggests that that may not be the case, that actually the half-life may be fairly similar in patients who got higher doses of lamivudine than those that got lower doses of lamivudine.

But, first of all, could you respond perhaps, or even the sponsor might respond first of all, about the dosage, the duration, and something of that order?

DR. BROWN: I mentioned on a slide -- I think it was called principal dose findings -- that in fact using either the conventional hybridization assay or PCR, we don't see any really appreciable difference in antiviral effect at doses in adults above 100 milligrams per day. The PCR data we have in adults extends essentially out to 6 months. In that particular European 6-month study, the doses that were compared were 25, 100, and 300. We have that data on a slide, but the bottom line is even when you use PCR levels, we don't see a difference in clearance of virus, if you will, at doses above 100.

I also mentioned that we don't see a difference in incidence of YMDD variants either in the progression modeling by dose, I should say, or drug concentration for that matter. We don't see a difference in YMDD variants in the regression modeling where dose was factored into it, nor did we see a difference in the Asian multi-center trial between the 25 and 100 milligram cohort. At 1 year in the 25 milligram, it was 14 percent incidence, and 16 percent in the 100, but that was very similar not statistically distinguishable.

But certainly I think we certainly agree, and a

major issue I think obviously for discussion is treatment duration. Here's the result of discontinuing lamivudine arbitrarily at 1 year for the purposes of studying the drug in patients with chronic hepatitis B. What we've displayed here are the post week 52 data across the three studies in which there as a lamivudine 100 milligram patient cohort, and placebo is illustrated in yellow.

First thing important to point out is -- I think it was emphasized perhaps in the FDA's presentation -- there is a decline in HBV DNA levels in placebo patients. And during the first year we showed that on our core presentation as well. That has actually been observed in the 3-month adefovir study recently reported as well. We think there may be regression of the mean operating in this disease that has a somewhat cyclic nature, but that's a speculation.

In any case, here's the placebo HBV DNA in the post-week 52 period, so to speak, looking about level. Here's what happens in the cohort. I mentioned we had an exploratory cohort in the interferon nonresponder study where patients stayed on drug, and this is their median HBV DNA level on that treatment arm where they stayed on out to the end of study at week 68. Here's the rest of the patients from the European/Canadian study, as well as the U.S. study, and half of the patients on this study who went

on to either placebo or just discontinued from treatment at week 52, again showing, as we observed in phase II, that the disease does come back in this case over a 4-month post-treatment period. So, the continuously treated lamivudine group in this kind of analysis did better with regard to viral load.

We have an ALT curve that basically shows the same kind of phenomenon with the ALTs tending to come back up towards placebo ALTs when you arbitrarily discontinue at 1 year.

DR. HOLLINGER: Yes, I see that, but again I think what Dr. Styrt presented was data with the seroconversion and that looked like that continued to improve as time goes on. I think the bottom line is you really don't have data which compares 100 with 300 for a year to look at whether there is a reduction in the variants or the response rate. Is that correct?

DR. BROWN: It's correct that we do not have 300 milligram dosing data for a year because of the considerations I mentioned. 100 milligrams was chosen as the phase III dose. I'll stop there.

So, with regard to effects of longer therapy on e conversion, we mentioned that we felt we were seeing some additional effects. In the 3011 study, we and the FDA mentioned that we didn't feel we had achieved statistical

significance for seroconversion in interferon nonresponders, whereas in treatment-naive patients in the Asian and U.S. study, it did appear as statistically significant. This is the 3011 study, and the seroconversion rate at week 68 in this study for the continuously treated patients was 24 percent compared to the 18 percent which we showed for week 52. So, that's another little bit of evidence where we think there may be some cumulative seroconverting effect. Actually in that study placebo stayed about the same. So, the difference between drug and placebo did get greater at week 68 in that study.

But I mentioned the paradox on that study was that that interferon nonresponder study actually had the highest e antigen loss rate at 1 year. So, the question is in this patient population, do they have a somewhat delayed development of antibody to e which affects the analyses of full conversion?

DR. HOLLINGER: While you're still there, have you had a chance to look at anything regarding the development of HCC in any patients?

DR. BROWN: No. We certainly have not been able to observe any kind of differences, and we saw no HCC in the core studies. It's an issue that I think we're certainly interested in looking at for some of the long-

term clinical outcome studies that we're anticipating.

DR. HOLLINGER: The other thing, I think an observation on the data that the FDA presented. It has to do with the seroconversion status versus histology. In a couple of slides, I think it was noted that even though some patients did not meet seroconversion criteria, many still showed histological improvement. And I wondered whether there might be a threshold for histological improvement that doesn't involve the absence of HBV DNA. Actually that would indicate potentially that you could have some HBV DNA replication going on and still generate a good histological improvement both in fibrosis, as well as the necroinflammatory response.

DR. BROWN: We do have a slide that actually the basic impact of which is similar to what Dr. Soon showed. Dr. Soon, if I interpreted the presentation correctly, showed that there's a pretty tight association between the seroconversion and histologic response, if you were using that kind of response definition. But he also showed that in patients who didn't have e conversion or serologic response, if you will, he showed histologic response in 21 of 37, which boils out to 56 percent, and that's very similar to our analysis as well.

We looked at the composite phase III data for patients who were still positive for e antigen at week 52

different because we don't know enough about the viral pathogenesis, given the limitation on the assays. A confirmed e antigen seroconversion does have some clear relationship to durability, and that's probably the only data we have.

Development of viral resistance at the moment is worrisome, but the data show that those patients at least in the limited follow-up still are doing better. They're intermediate between placebo and the wild-type. So, I think one wouldn't stop if one were getting a YMDD mutant. One would just worry about it.

And as far as reappearance of viral DNA during therapy, again I think it depends on the threshold of your assay and assays that are looking at thresholds of 10 to the 5 and 10 to the 6th are again, to quote a refrain from another disease, the tip of the iceberg, and getting below detectability is going to, I think, have a much greater lower limit target of 100 copies when we're there.

Also, as far as stopping for the development of resistance or reappearance of viral DNA, that's really an issue of the options one has as well as the assays, and when one has limited options in this disease, one is probably not going to stop.

The optimal duration of treatment for patients I think is not clear. That only will come through follow-

up studies.

The implications of resistance I think are ominous. We need to know more about it, really what the preexistence of viral mutants is. It doesn't seem to be high, but we need to know more about the sensitivity of these assays that are looking for resistance both in the blood and in the tissue. It clearly is going to limit the drug over time and is another reason once again to move quickly into combination treatments.

I think that the approval of this drug is going to change things because placebo controls are not going to be, at least to me, permitted in this population. So, one thing we have to think about is if we have new active control arms, are those active control arms going to be monotherapy arms for a long time or should we be, in fact, thinking about novel ways to do active control arms that quickly move into combination status.

Dr. El-Sadr raised the issue of the reintroduction of treatment and whether resistance will really emerge, and I would echo that. It's nice that the viruses that come back after treatment stops in the setting of resistance are wild-type, but we have no reassurance and probably it's quite likely in this setting that resistance will quickly reemerge.

The point about relationship of virologic and

serologic markers as a proxy for histologic changes. I like the term "proxy" because it particularly avoided the issue of surrogate markers which has taken this committee around in circles in the past, but that's essentially what this is about. Again, we have to improve our assays and have our correlations with histologic outcome, but without long-term follow-up for the longer-term outcomes, we won't really know. But obviously it makes sense that if you get improved ALT, drive the virus to undetectable levels by hopefully newer and more sensitive assays, and get seroconversions, that's all very logical and I think we have enough data to make the prediction that that's going to be good for patients in the long term.

As far as the HIV issue, I agree that it should be mandated. You really can't mandate it, but one thing it should be is standard of care and it also should be included in the label. I'm sure it will be, but caution should be exercised before Epivir for hepatitis B at 100 milligrams per day is prescribed, that HIV status be determined.

One thing we should recognize, as far as this goes, is patients at risk for acquisition of hep B are also at risk for acquisition of HIV, as has been stated. That's an increasing issue for patients not just in accident situations but in other situations of sexual or other

exposures where people are now thinking about prophylaxing. We've been prophylaxing with hep B with other things. We now are prophylaxing HIV in emergency rooms and elsewhere, and 3TC is a major component of that. So, it's an interesting ponderable here to think about what the role of this agent is in prophylaxis of hep B and when it's used also to try to prophylax HIV.

So, I hope that helps. I think basically there has been a strong consensus among the group here that we need longer-term outcome, other studies, but that this is a significant and important step, an incremental step, but a major incremental step in the treatment of an important disease and that we have learned a lot from other diseases, and we need to apply that to hepatitis B and antiviral therapy.

Is there anything else that we need to address?

DR. JOLSON: No. I think we really appreciate all the advice that we've heard today. I think it will be possible to envision phase IV commitments that will echo the issues that were brought up here in terms of where additional information is necessary.

I think the major issue for us that remains -- and obviously there's not available data -- is the issue of treatment duration and how that's going to be approached in the labeling. This is really a major departure for us from

the interferon model where interferon is recommended for use for a certain duration of time and after which a patient is observed and either has a response or doesn't. And the labeling can deal with that.

This is going to be somewhat more difficult and is really going to require I think some negotiations between us and the sponsor in terms of what is the optimal recommendation that can be made in the label given the lack of information about the optimal treatment duration.

One of the problems that I foresee in recommending that patients be treated until seroconversion is, at least based on available data, seroconversion occurs at a fairly low rate, and it may keep patients on therapy who are no longer deriving benefit. Exactly how we will deal with that in the label to prevent just continued year after year of drug exposure in patients who are unlikely to seroconvert based on response to drug, I kind of see that as a challenge.

DR. HAMMER: I think the seroconversion is perhaps one issue where we have data to suggest that the response is durable, but it shouldn't be the only criterion. I think this is going to have to be a flexible issue in relation to other markers of response, and one could list a number of markers of response. Again, as assays improve, this will be helpful, but ALT,

seroconversion, hep B DNA. One could probably make a recommendation that return to baseline in all of those elements is probably evidence of lack of response or loss of response, and one could stop there, but I don't think personally that any single test is going to be able to be used to be sure that you want to stop except perhaps the seroconversion for which there is some data. But I think that's likely going to be supplanted by a combination of markers, including a more sensitive hep B DNA assay.

DR. JOLSON: So, just to make certain that I understand what you're saying, then you think it would be reasonable to recommend other criteria for when lack of response should be considered.

DR. HAMMER: I think at least for the current label or the imminent label, stating what the data suggest as far as e antigen seroconversion is probably where to start, but to say that there are other considerations as far as viral markers in the absence of liver biopsy, which are not going to be done routinely in the clinical setting, that consideration should also be given to these other markers as far as measures of response, although the data do not currently exist to be certain about the long-term relationship. I think there will have to be some flexibility in that because, in fact, that will foster I think clinical care that's more in keeping with what the

data suggest.

That's just my opinion. Others can comment.

DR. JOLSON: Any other parting remarks about recommendations for stopping therapy?

DR. HAMMER: Given the expertise, particularly of our guests and consultants, it just reflects that we need more studies and the lack of the current database.

DR. JOLSON: Could I just ask one other question about for future studies for this agent or other agents? The way studies had been designed, and remembering that these studies were designed several years ago with more the interferon model in mind, with a specified treatment duration, after which, at least in one or two studies, treatment was discontinued and patients were observed, in light of this information, do you have recommendations for trial design for other agents in this class?

DR. HAMMER: I'll start because I'll reveal a prejudice. I think although it was an advance, we've been hamstrung by the interferon experience and those initial trials because then it became the control arm, and it doesn't make sense to have this very delimited period comparing 16 to 24 weeks versus 52 weeks of another agent. And I would suggest that we need longer and equal treatment arms as far as duration goes in future studies and that we

should try to move away from the classic interferon course as the standard of care. I think the ultimate approval of Epivir will change that and for the better. I think we need longer treatments. Interferon can be moved into that in new ways perhaps, but I also think the toxicities of interferon, as we get new agents in the next 2, 3, and 4 years, may move that to a second-line agent.

DR. SO: I think Heidi has a tough job. Do we have enough information to say that after 3 months of treatment, if DNA does not come down at all, those patients should be taken off of treatment? I mean, it's sort of a treatment guideline as to who are responders, who are nonresponders.

DR. HAMMER: I think we tried to get that question. There are some data that could be looked at as far as early changes in markers and predictors of response, and I think those data need to be culled out of the current database. One would think that if one has no early response in any marker, including hep B DNA, I would think logically it's time to think about something else if you've got it.

DR. SO: Just one comment because I see a lot of patients who come to me already taking all sorts of things like shark's cartilage and all these other treatments for hepatitis B, and some of them would like to

stop the drug and then switch to a different agent. I hope the sponsor will really clearly label or really emphasize that stopping treatment unsupervised could lead to a flare-up in their hepatitis because I think a lot of the Asian population like to switch drugs and they might end up with a big problem. Thanks.

DR. HAMMER: Dr. Yogev?

DR. YOGEV: I don't know. If you allow me. I was a little bit impressed maybe more than you that the interferon really didn't work, and I would encourage to go into know synergy studies which we show at least in vitro the two nucleosides and so forth.

DR. HAMMER: That's what I think I was saying that interferon is going to fall by the wayside.

DR. YOGEV: I would encourage not to use that at the start and really to go to 52 monotherapy which is dual therapy just because we have the monotherapy.

DR. HAMMER: Well, I think it's going to be combinations of interferon and Epivir, Epivir and other nucleosides, Epivir and nucleotides, even three-drug therapies for severe disease. I think we'll see novel ways to look at these, but interferon isn't going to leave the combination therapy yet. It needs to be studied in other ways that disprove that it's not any better than single agent therapy.

DR. YOGEV: And the other point is I thought maybe it would be good at least to draw the attention of the physician that if the HBV DNA is going up, that efficacy has a tendency to be less than if they're staying down. It's a point to start reassessing therapy. If we won't put it in the insert, nobody would think about it. They would just continue doing it because we have nothing else to do. That's what we did with AZT, as you very well know.

DR. HAMMER: That's where the new options will help.

Blaine.

DR. HOLLINGER: Yes. As distinct from, say, hepatitis C, in which we know there are more resistant genotypes available, it doesn't seem to be that way for the HBV DNA. I think we saw data today which said that the YMDD is not seen in the placebo group by and large. Therefore, almost all these patients respond to therapy. At least their HBV DNA goes down very rapidly, within 4 to 8 weeks, in most patients. Now, whether there is a small subgroup in there which we could look at very carefully to see whether or not we could determine who will have a sustained response I think is open for question. We need to do that. But whether we'll find something like the 3-month cut-off level like we have for interferon and HCV is

another issue.

My take-home message is that these patients need to be treated probably for at least a year, and that's sort of the take-home message I would have, unless they seroconvert from e antigen to anti-HBe in which case, if I saw that over one or two times, at least a couple of times, I might feel comfortable in discontinuing therapy in that individual based on the durability of the response that I have seen in the data presented.

What I don't know is just what you've said, is what do I do after a year? Because it seems like between a year and 2 years, you start seeing a difference between an increase in the HBV DNA based upon resistance developed and response. It's that question as to whether you go on for more than a year, but at least a year it seems to me is of benefit in these patients, possibly 2 years.

DR. HAMMER: Thank you. I think on that expert note, on behalf of the committee, I'd like to thank the guests and consultants, the sponsor, and the agency for a very interesting day.

This session is closed.

(Whereupon, at 4:00 p.m., the committee was adjourned.)

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when the biopsies were done, and in fact we did see a histologic response rate somewhat similar to what Dr. Soon displayed. I have it on a separate slide, but the concept is the same. So, we do see histologic response, as you're indicating, in patients who are still e positive.

DR. HOLLINGER: Finally, did you look at any evidence for lactic acidosis at week 52 and particularly at the period of time that's the end of treatment or in the follow-up period when these patients had what looked like flares of their ALT? And also then maybe Dr. Goodman could tell me also whether there's any change in the steatosis levels in the biopsies that he saw at the end of treatment.

DR. BROWN: We have a slide on this issue which obviously is, in a sense, an au courent kind of safety issue within the HIV area.

It's fair to say we didn't see any of what you might call full-blown cases of the lactic acidosis, steatosis syndrome that's being investigated in HIV patients on combination therapy.

Probably the best thing is to go to the slide on this one where I summarize what we found.

Another part of the answer is that we didn't systematically monitor blood lactate levels, but instead, these are basically the findings on this issue.

First of all, obviously particularly in the

transplant patients, but really in any large group of patients as we enrolled in this program, there are a number of things that can be associated with metabolic and lactic acidosis, if you will. And just briefly recounting this, this is actually Harrison's Textbook of Medicine. If Dr. Fauci is here, I apologize if it looks like he's being directly quoted, and there's a misspelling of Braumwald.

In any case, so there's a lot of background on this kind of issue that obviously most people in the audience are aware of. Some may not be.

We didn't see any cases of the full-blown syndrome in our total development program, including the non-core studies as well. What we did see were two cases of lactic acidosis. One patient was actually asymptomatic. The liver biopsy was normal. The patient did go off treatment, but the reason for the lactic acidosis in this treatment was never really clear. Eventually it cleared.

The other patient was a patient obviously with advanced liver disease, cirrhosis, variceal bleeds. And unfortunately, we had minimal information on this patient. A lot of these things are included up here in terms of things that can give you acidosis.

We saw six other cases of metabolic acidosis, and the bottom line here is all patients were in the advanced disease, open-label kind of transplant studies, if

you will, and they all had underlying conditions. Sometimes there was documented sepsis, all the rest of it.

DR. HAMMER: Can you just remind us for the record of the denominator of all exposed patients in your program?

DR. BROWN: Well, there's a little bit of overlap on 1,300 number that Dr. Rubin showed in the follow-on studies because those are obviously patients that were studied in phase III and then carried forward. I may need statistical help on the total denominator there. Not counting the compassionate use studies. Is that correct?

DR. HAMMER: Can anyone help? Brought out 52 weeks or longer I think to answer Blaine's question.

DR. BROWN: Right.

DR. HAMMER: To put the slide in perspective. Ball park figure.

DR. BROWN: Yes, I can give you some approximations. There's approximately 2,500 compassionate use patients most of whom were advanced disease patients in the U.S. and Europe. It's hard to say what the median is at this point, but a good number of them, probably over half, are on a year, sometimes up to 3 or 4 years, of treatment. So, that's our compassionate use data which is being monitored centrally to some extent.

And then in the sponsored program, we have

something under 1,900 total patients or so. A fair amount of data at a year or more. Of course, in the HIV arena, thousands, but that's a different issue there.

DR. HAMMER: Thank you.

Please, Dr. Yogev.

DR. YOGEV: Excuse me for reiterating the resistance issue. As much as until now I didn't want to think about HIV, I think this story is reminiscent of what we did with AZT, ddI and so forth. We're checking off to 10 to the 5, 10 to the 6, and we claim we know what we're doing and we have much below the curve.

What was interesting to me, when you presented data, at 24 weeks the DNA are reappearing in many patient indexes after the same time you start seeing the resistance coming up and going up. To me there must be something connected over there that I don't understand why, if we increase the dose -- and we know that the dose in HIV is higher -- in a virus which is about the same rate to start with, 10 to the 8, 10 to the 10 or whatever, we should not see some data to that.

The other question for the FDA. In special populations, for some reason you didn't mention at all pregnant. Are we going to ignore them or this is a population we would like to see some data? Those women had a flare-up of the disease. That's where disease is coming

out. I just wonder if any plans or you want to?

DR. STYRT: I think it's safe to assume that we're always interested in particular special concerns that might be applicable to pregnant women.

DR. JOLSON: And also these are the sorts of issues that if there were no data available now, which I assume that there's probably not, that you all could make a recommendation to the sponsor that they be addressed, presumably as phase IV commitments. Whether it's looking at higher doses, looking at special populations such as safety and efficacy in pregnant women, those sorts of things are all very appropriate recommendations. And I think as you get into the questions, you'll have an opportunity to reiterate some of these issues.

DR. YOGEV: And the last quick point. One of the committee asked about the length of the disease for the time that the study started. Did you look into those who were vertically transmitted? Where was your time? It's around the time they were born. So, if we take the age of those patients at the time of the study, we can find out how long they have chronic hepatitis might have any effect on the outcome. Was that done?

DR. STYRT: Again, as you've seen in the initial slides, most of the patients -- the most popular reason for acquiring hepatitis B was unknown in these

studies. I know that the sponsor has looked at things like age breakdowns and may want to comment on that further. But I think with the largest subgroup of people not necessarily having a known time of acquisition, it could be somewhat difficult to draw conclusions in the current state of affairs.

DR. HAMMER: Thank you.

I just have two quick questions, another resistance question. Has there been any amplification out of the tissue at 52 weeks to look for YMDD mutants in the tissue that may not be appearing in blood yet and if not, are there plans to do such?

DR. BROWN: The first answer is no. It's very difficult to get tissue on multi-center studies, as you can imagine, particularly with a procedure that has a 1 to 3 percent serious complication rate.

DR. HAMMER: As part of the routine biopsy, PCR, you don't need a whole lot.

DR. BROWN: Right. So, it's an excellent scientific question and we've certainly talked about potentially doing some tissue studies. Getting representative samples and appropriate cohorts is a problem when you're trying to get enough information to draw a scientific inference. That can be a problem.

DR. HAMMER: I raise it because I think you can

sense from the committee and our discussion later will focus a lot on the issue of resistance. So, as much scientific information as can be derived over the next several months to years will be critical.

DR. BROWN: Sure.

DR. HAMMER: One follow-up question to special populations that were alluded to earlier and briefly mentioned in the packet, and that is, have you teased out the HIV subpopulation in your studies? And can you say anything about response that may or may not be different or the same?

DR. BROWN: Right. Patients co-infected with hepatitis delta virus, hepatitis C virus, or HIV were actually excluded from the core phase III trials in order to not have confounded analyses. So, the answer is no. We obviously won't be able to tease out those data from the controlled trials.

We do have a little bit of data in HIV/HBV co-infected patients, a retrospective analysis of safety data from the CAESAR study, and then of course a brief encapsulation of the Annals of Internal Medicine publication of Benhamou from November 1996. But we specifically excluded C, delta, and HIV from the core patient population in order to study the effects just on hep B.

DR. HAMMER: But even going back to a study like CAESAR, you looked at safety but you didn't look at serial specimens to see what their DNA was doing or anything.

DR. BROWN: I think we can say as an exploratory thing we did not look in CAESAR, no. One of the investigators did and there seems to be an antiviral --

DR. HAMMER: I raise it because it's one of the questions in part posed to the committee. So, I wanted to give you an opportunity to comment.

If there are no additional questions for the sponsor or the FDA --

DR. SO: One comment. As a caregiver for many Asian patients, it's encouraging and also interesting to see that from the data presented this morning that the most significant -- the group that showed the most significant improvement is actually the patients in the Asian studies.

My question to Greg and Barbara is, do you think it's because that study has the most complete data? Is it because the other studies have so much missing data that it might not show as significant a difference?

DR. SOON: Certainly the number of missing are much less in the Asian study. I don't know what's the reason for that, but certainly that helps to make the conclusion more certain.

DR. SO: Because traditionally that group of patients is the most difficult to treat because most of them do not respond well to interferon therapy.

DR. STYRT: I think there are so many ways in which this study could speculatively be said to have differed from the other studies. Of course, if one of the other studies had been different, we'd probably be coming up with reasons why that study might be different. I think it would be extremely difficult to try to say that there is a definite reason. In fact, as the sponsor has pointed out, it would be rather difficult to say that there is a definite and obvious difference.

We felt that there were ways that in the exploratory analyses, this study looked different from the others and that we would be interested in whether it was possible to derive more information that would illuminate that apparent series of distinctions. But I don't think that we can definitely say there is a difference in the way this drug affects different populations from the data that has been presented, only that there are some further questions that we think might be interesting and useful to explore.

DR. HAMMER: Dr. Lee?

DR. LEE: Actually I'm from Calgary and in response to the question Dr. Hamilton posed, 10 percent of

our population is Asian immigrants, a fact which has always amazed me considering that it's way up by the base of the Rockies in Canada and the worldwide perception of Canada is that it's always freezing cold and polar bears roam the streets at will all the time. So, it's amazing that so many Asians settled there. But I do have a fairly large practice of Asians.

I think a couple of things that I'd like to comment on, and I think it's clear that there's a major difference in the natural history between Asians and caucasians because one is neonatally or infant-acquired and one is adult-acquired. Clearly these entities differ, and it's not a racial or ethnic thing because Eastern Europeans with neonatally acquired disease behave like the Asian chronic carriers. So, a lot of this data I think can be explained on that basis.

The second issue I'd like to raise is actually the issue of the New England where the Claus Niederal paper was published also contained a very thoughtful editorial I think by Ron Coritz which had a number of good points about it. I think he was playing devil's advocate. But here we have a disease that in the majority of people does not cause morbidity or mortality. Somewhere between 15 and 40 percent of patients, the minority will get some complication, maybe cirrhosis, maybe cancer, and die from a

complication. But if you wait long enough, almost all patients who are chronic carriers in this category will seroconvert into an e antigen negative/e antibody positive form.

And the question Coritz asked and I think we should also be asking in a forum like this is, what are we accomplishing with any type of intervention? If the majority of people are going to seroconvert on their own after 1, 2, 5, 20, 30 years, is this therapy going to be useful?

I personally think the evidence that has been presented today answers that as yes, but yes, it will be useful to shorten that duration of replicative stage, immune intolerant hepatitis B activity, and hopefully with the logic that it will prevent progression or decrease the rate of progression to cirrhosis in liver cell cancer. So, I think this is an important advance, an important drug.

DR. HAMMER: You've answered question 5 already for us.

(Laughter.)

DR. LEE: Sorry. I didn't realize there was further -- but I have a couple of quick questions and perhaps I'll delay them if this is also going to turn up.

DR. HAMMER: I would just say that these are for information for us to discuss later, questions that you

have to the sponsor or to the FDA for informational purposes, but we have the next round to expound on our feelings.

DR. LEE: Okay.

The question to the sponsor or perhaps one or more of the investigators involved in the trials, is eventually when we start using this drug, there's clearly histological nonresponders and e antigen nonresponders. They have suggested the endpoint of using it as waiting for an e antigen seroconversion. Could we get some guidance on the histological nonresponders? When do we stop treatment?

DR. BROWN: Let's try M-43. This is a key observation within our program with regard to the factors which may influence histologic response, and in a certain extent, it relates perhaps to Dr. Hamilton's question earlier as well.

What we found was the key baseline factor that in a sense interacted with our ability to measure histologic response was in fact baseline Knodell score. The good news is, as patients get more and more severe disease, the numbers get smaller, but the response rates get fairly high. Now, some of these patients may be patients who may be serologically flaring and so may be seroconverting, and the numbers get smaller and smaller.

But one of the things that influences one's

ability to measure histologic response is baseline Knodell score, and we feel that in patients with quite aggressive disease -- I could show you I guess -- here's another good example. I think hepatologists in the room are used to thinking about cirrhosis as being something that may actually preclude response in some of the previous trials. Here we see the histologic response status by baseline cirrhosis status. In fact, again the numbers of responders are obviously a lot smaller for placebo. Here's the lamivudine group, and what you see is in fact no difference. Cirrhosis does not preclude response to the drug.

But I guess your question to some extent is a hypothetical one. In somebody who has no histologic response and no e conversion, I think our data would suggest that is more likely to be somebody who didn't have a lot of histologic disease to begin with. That's a clinical judgment on whether you treat that patient or not in a nutshell because that's likely to be a patient with fairly mild disease.

I'm not sure if I answered your whole question. There was another side to it that I probably forgot.

DR. HAMMER: Dr. Fletcher.

DR. FLETCHER: I know this will be an issue. I suspect it will come up in the discussion, but I would be

interested in hearing some response from the sponsor on this issue of the dose difference between lamivudine for HIV and lamivudine for HBV and what you would propose to recommend to a practitioner, to a patient that is co-infected with both viruses.

DR. BROWN: Yes. We're certainly recommending that patients who are co-infected get the HIV dose of lamivudine, needless to say, which is the 300 milligrams per day rather than 100.

DR. HAMMER: Blaine. This is the last question.

DR. HOLLINGER: I was impressed with that. Show that last slide again. Am I interpreting this correctly? Patients who have very bad liver disease at baseline, even the placebo group, have a very large response rate.

DR. BROWN: Well, you get a lower number of responders in placebo, but in fact the improvement in patients with what you might call very histologically aggressive disease is easier to measure. But again, the caution here is, as you break down data into subgroups, as is always true, you can get misled sometimes by one's tendency to draw inferences.

But, yes, we are saying in a sense patients with pretty aggressive disease or with cirrhosis, in fact,

do appear to respond reasonably well. Those don't preclude a histologic response. Somebody who doesn't have a histologic response is most likely to be somebody without much histologic disease to begin with.

DR. HAMMER: I'm sorry. I ignored Wafaa. Do you have a question?

DR. EL-SADR: I have a question. It seems to me that the population you enrolled in your studies were quite diverse, some with pretty mild disease. Like, for example, in the 309 study, which I think is the study in Asia, the ALT is 1.5 the upper limit of normal.

DR. BROWN: Right.

DR. EL-SADR: And there are other parameters. They appear to be the least at risk for progression, based on these parameters.

As you're thinking down the line of who would be the person to treat, are we here talking about treating everyone in the world who has hepatitis B, who is a carrier, who has any detectable HBV? Because not everyone also got a liver biopsy at baseline. Or are you thinking of a subgroup of patients, and can you define that subgroup?

DR. BROWN: Sure. Let me say two things. We're not recommending treatment of healthy carriers. We can say that flat out.

The kind of data that was referred to today, the 15 to 40 or the 25 to 40 percent of patients who might get serious disease, that's not predicated on the patient population we've studied. That's predicated on just overall chronically s positive people. The population we studied are patients who previously demonstrated high risk for progressive disease within that chronic surface antigen group, namely patients who are e antigen positive. So, the kind of disease development rates that you heard about are probably higher if you're treating s positive/e positive patients because those are the high viremic patients who are much more likely to get the progressive necroinflammatory liver disease, and those are the kind of patients that we're targeting.

It turns out that, when you look at those patients, as we mentioned earlier, even in patients with normal ALT, who are one-third of the Asian study, a fair number of them have histologic disease. In that particular study, we did look at patients with normal ALTs. As I mentioned, their median HAI score was 5. So, in that subgroup within the Asian study who had normal ALTs, there was good evidence that a fair portion of them had some histologically active disease, median HAI score of 5.

Now, that's not the same as documenting, as has been done in other studies, someone who is a surface

carrier with normal ALTs for 2 years or 5 years or whatever.

DR. STANLEY: Sorry. I'll make it quick.

DR. HAMMER: Please.

DR. STANLEY: But I was struck by that slide also, Dr. Hollinger, but by the number that 73 percent on placebo improved in the most severe disease. Is that telling us that our criteria -- that means they improved 2 points on the Knodell scale -- that that's not strict enough or rigid enough to really give us a treatment effect?

DR. BROWN: Let me say it was number of responders, but it was the number of placebo responders within that category. The overall number of responders was much smaller for placebo. If you analyze then the subcategories by baseline Knodell, the influence within the small group of placebo patients who responded, the influence of baseline HAI is similar to what you see in lamivudine when you subcategorize them by baseline HAI. I'm not sure if that is what you're referring to, but the overall histologic response rate is what you saw and what Dr. Soon demonstrated as well.

DR. HAMMER: I think it illustrates just again the variability in the measurements in this disease over time on an individual basis perhaps and it can influence

study interpretation.

Dr. Jolson, did you have any comments to the committee before we attack the questions?

DR. JOLSON: No.

DR. HAMMER: Thank you very much.

It's now the job of the committee to respond to questions posed by the agency. What I'd like to do is pose the first question initially and defer the others till after we've discussed this. I'll read it for the record.

Does the information presented by the applicant support the safety and effectiveness of lamivudine for treatment of chronic hepatitis B? If the answer is no, what additional studies are needed? If the answer is yes, we will go on to questions 2 to 6.

I'll start on my right with Dr. Masur.

DR. MASUR: I think clearly the data support the safety in the population that has been studied. Again, there are clearly patients at one extreme of severity where one could desire more control data. But there isn't an issue in my mind about the safety of this data and the doses that they're looking at.

In terms of effectiveness, I think there's convincing surrogate marker data that there is an effect for a discrete period of time. There's data that there is clinical -- or there's data at least that there's

histologic benefit during that period of time.

I guess the concern that has been voiced is how durable this effect is and whether or not it really changes the long-term history of the disease. I think it's very hard to determine from this database whether further out than a year there really is a benefit.

Ultimately I think we're all going to wish that there were longer-term data showing that there was histologic and at least enzymatic benefit. Again, the issue about harder clinical endpoints in terms of clinical events and death is very hard to come by.

So, I guess overall, given the dearth of useful alternatives, I think that there is enough data to support effectiveness. I'd be willing to support that assertion. However, I'm very concerned that we need a lot more information about how to use this, how to avoid losing the efficacy over time, and exactly when to intervene.

DR. HAMMER: Thank you.

Dr. El-Sadr?

DR. EL-SADR: I agree with Dr. Masur. I think the safety is very clear from the data presented today. I think the sponsor did look at their primary outcome for their study and they did demonstrate the histologic difference between the two arms of the study.

I'm very nervous and very concerned about what

it all means and whether in a year or 2 years we'll be sort of again wondering if we're doing a lot of patients any favor by maybe this short-term response.

I'm concerned about the dose. I think I'm very concerned about the dose and whether this is the optimal dose for treating this infection and especially with the associated mutants arising on therapy.

Nonetheless, I think that the study did answer appropriately and positively the primary outcome that was designed in the study.

DR. HAMMER: Thank you.

Dr. Diaz?

DR. DIAZ: I likewise would agree with the two prior comments. In particular, the safety is quite readily available in adults, and it doesn't answer questions for, for instance, long-term users, but over the period of the study, I don't have any doubts about the safety of the drug.

The efficacy, likewise, answered the questions that really was the histologic endpoints of the study, and in that regard, certainly I think the proof of efficacy is there but likewise laud some of the concerns about what that means overall long-term-wise, what it means in different groups of patients and likewise the concerns about having variable serologic and virologic data and what

that will mean in the long run.

But in terms of the study design, I think the safety and efficacy is there.

DR. HAMMER: Thank you.

Dr. Hamilton?

DR. HAMILTON: To me the sponsors have assembled on an impressive array of clinical trials to support their application for licensure both in terms of efficacy and safety. I too am convinced that safety has been more than adequately addressed and by all means should be continuously followed but would warrant its use on that basis.

Having said that, I believe the sponsors have also provided us with ample evidence, given the rules of the game by today's standards, that this agent will, by surrogate marker analyses, alter the course of their subsequent illness.

I remain very concerned, however, on a number of points. There's still a lot of virus present. I think Dr. Hollinger pointed that out and others have as well. And increasing amounts of virus apparently in patients on treatment. It's very worrisome to me. And in combination with or in parallel with, these emergent strains of mutants are appearing now even before licensure of this drug. With AZT at least it took a little while until the drug had been

given. Now we know it in advance, and the level is very, very concerning to me.

Though I'm reassured by the comments of the expert hepatologists in the room that the quality of life, both short-term and longer-term, would be modified by the availability of this drug, there in fact have been no objective measures of that benefit. But I'm satisfied that certainly in making individuals eligible for more aggressive kinds of interventions like transplantation would in itself be useful.

Another perspective from which to view the prospects of a given drug I think revolve around its role in the public health. I guess the major focus here today has been on that of the individuals infected to date. I would that to that, however, several other populations that perhaps we haven't thought in as great a detail about, and that would include those who may be uninfected as of now but in positions where they might become infected, i.e., sexual partners of known infected patients and obviously newborns of infected mothers. I'd be reassured if I knew that such studies actually had already been done or were in the process. I think they're extremely important. Limiting the infectivity of patients could be in and of itself sufficient indication for use of this drug.

It's a long-winded way of saying that I believe

this drug should be approved but looked at from a variety of other perspectives in subsequent months and years.

DR. HAMMER: Thank you.

Dr. Yogev.

DR. YOGEV: It's always unfortunate to be the sixth in a row to say the same thing.

But I think I would agree with my astute colleagues on the committee for adults. I don't think we have near the safety nor efficacy in pediatrics. That should be clearly stated in that recommendation and, in addition, adolescents, although we don't know where to put them. The pediatricians claim they are adult, and the adult claim they are pediatric. So, I think they fall again in between those two, and we don't have data.

Also I think it would be very important to suggest -- and I'm again unfortunately reflecting from our bad experience with HIV on those drugs -- that it's going to be for a limited period of time in the majority of patients, and we are going to see a small section of the population which will really enjoy it because we are moving the bell curve probably a little bit to the right. But we need to make sure that it's not taken lightly that it is a wonder drug for everybody.

DR. HAMMER: Thank you.

Dr. Stanley.

DR. STANLEY: Well, I guess that's my biggest concern, is what did we learn from the AZT fiasco, shall I call it, or experience.

I'm convinced that, yes, they've shown safety in adults. We don't know enough about the pediatrics, but I'm very concerned about the durability of the effectiveness when we're already seeing in a large number of these patients DNA reoccurring, reappearing, and the resistance developing. So, I'm very concerned that if this is the ideal dose, then it is clearly not able to effectively suppress viral replication to prevent mutants from appearing. And it would suggest to me that we need a multi-pronged approach to this disease, and we may do more harm in the long run to patients by allowing them the opportunity to develop resistance to this single agent.

DR. HAMMER: Thank you.

Dr. So?

DR. SO: I'd also like to echo the same sentiment as the previous speakers. Clearly this seems to be a very safe drug. At least in the short-term it seems to be just as effective as interferon and maybe more so in the Asian population which acquired the disease, most of them, early in life. I think it should be made available for transplantation.

But I also am unclear about the long-term

sequelae of the development of these YMDD mutants. I hope the sponsors will continue to support long-term studies to see what happens to these patients and whether long-term treatment also will help to decrease the incidence of complications of cirrhosis and hepatocellular carcinoma.

I also feel that, yes, we really need more data on the pediatric population before that should be approved for the pediatric patient.

DR. HAMMER: Thank you.

Dr. Lee?

DR. LEE: I thought I didn't get a vote.

DR. HAMMER: You can comment. You won't get a vote, but you certainly have full ability to comment as a guest expert.

DR. LEE: Well, like Yogi Berra said, just like deja vu all over again. I agree with everything that has been said.

I think the situation here can be likened to the company and the community of hepatologists and infectious disease specialists that treat hepatitis B. It's like a 5-year-old kid that has just been given the keys to a brand new Ferarri. He's sort of vaguely aware that he's got something great on his hands. It will take him 20 years to figure out the ins and outs of how it works.

DR. HAMMER: Dr. Sjogren.

DR. SJOGREN: Well, in thinking and rethinking about the whole issue, I think we could decide to look at the glass half full or half empty.

And certainly I echo my colleagues addressing the point of the YMDD mutants, and I think we need to ask the commitment of the sponsor to look a little more into it.

Also, the safety and efficacy, although very well established in certain populations, it has not been in some others, and that needs to be brought out, such as my colleague said, the pediatric population, the pregnant population.

Also, people that have delta infections have not been studied. Patients that have decompensated cirrhosis, perhaps child's B or child's C, those need to be addressed. I understand the limitations of doing that, but it still needs to be addressed.

We must also look at the benefit of the drug in other kinds of mutants. I don't think in the discussion it came out in the morning that the pre-core mutant is something that we deal with as hepatologists all over the world. My reading of the materials, the drug is very good for the pre-core mutants. So, indeed, there is a positive effect in there for some other type of mutations of the

virus.

I feel satisfied that the safety and effectiveness of the drug is good in the populations that have been studied, but not in the ones that have not been studied for obvious reasons that were explained to us.

Also, I want to borrow what I know of e antigen to antibody seroconversion from the interferon trials, and there are hepatologists in the room that can correct me if I'm wrong. But when seroconversion occurs after therapy, it's very sturdy. We have long-term studies in interferon trials, 6, 7, 8 years, a couple of them published in the literature, and when you seroconvert, you are 90 to 96 percent likely to remain seroconverted and with normal ALTs 7, 8 years down the pike. So, I'm not that familiar with the AZT phenomenon, but I am familiar with interferon and hepatitis B and I know when I see a seroconversion following interferon treatment, I feel very good about it because I know it's going to be a longstanding response.

Obviously, the sponsor, as well as the investigators, need to continue to follow up and tell us if this is true for lamivudine or not. My hope is that it is because it is a hepatitis B responding to medication.

So, I think although there is some nervousness about it, on the other hand I feel a little bit safer knowing or hoping that it will be a sturdy response.

DR. HAMMER: Thank you.

Dr. Hollinger.

DR. HOLLINGER: I also believe that the information provided by the applicant has supported the safety and efficacy of lamivudine in the treatment of chronic hepatitis B.

What we have here is primarily a remission with a small number of patients perhaps engendering a cure, but at least a remission. And the durability of response, as Dr. Sjogren has mentioned, does seem to reasonably good and probably will be long-lasting in most patients. We do have data from Dr. Liaw in Taiwan and others too which have looked at individuals who have gone through a remission. Their survival is improved over ones that do not go through a remission. So, I think we could probably guess that these patients that have a durability of response should have an enhanced survival.

In addition, I'm encouraged by the group of patients that do develop the YMDD mutation. It does appear that they have some benefit, and that when the drug is discontinued, most of these individuals will revert back to the wild-type virion. So, I'm encouraged by both of those things. There was a lot of concern that this resistant mutant would make these patients resistant, that they would actually perhaps be worse, but that doesn't seem to be the

case.

So, I think the applicant has provided support for the safety and efficacy, at least short-term efficacy, of this drug.

DR. HAMMER: Thank you.

Ms. Melpolder.

MS. MELPOLDER: In addition to what everybody else has said, looking at it from a patient's point of view, if I had no other options but lamivudine, I would want lamivudine if it was going to improve my quality of life.

The other thing is that when we looked at HIV, we had a drug, and then we found other drugs coming down the pike, and it got faster and faster. And I think that's what we're going to see with the HBV story.

So, I would want lamivudine available to me.

DR. HAMMER: Thank you.

Dr. Fletcher?

DR. FLETCHER: I also believe that the sponsor has met the safety criterion and the effectiveness criterion. I think like the other members that have spoken, I have concerns about our ability to offer a set of clear and convincing recommendations to patients, to practitioners about how the drug can then be used in the most effective manner given the heterogeneity and response

that has been observed -- not all patients have an initial response -- the durability and the emergence of resistance.

DR. HAMMER: Thank you.

If it's difficult to be the 6th speaker in line, it's even more difficult to be the 13th, but I'll be brief.

I certainly have no questions about the safety profile of this agent as presented and given the broad HIV experience at a substantially higher dose. I share all the concerns that have been mentioned so far, in particular the response rates which we would hope would be better and the durability and the issues of resistance. We don't want to take the analogy to HIV too far, but in fact it's quite helpful here in the sense that we're essentially dealing with surrogates of long-term outcome, whether they be the tissue marker, inflammatory and fibrotic marker evidence, or serologic markers, and we're being asked to look years down the line, knowing that in fact we can't wait necessarily for those trials before approving agents such as these.

I think we can also learn that we need to know a lot more about the viral pathogenesis of HBV. We need better assays to do it. We need to learn more about the resistance. For example, given the density of virions and the proposed turnover of HBV, why is resistance taking

months to develop? Why isn't it faster in the YMDD region? We don't know the answer to that and some very interesting possibilities may emerge. I think as we get more sensitive assays, maybe in fact it will be a high proportion early, but if it's not, then we'll be learning something very important about this disease.

It has been said many times -- and it's clear -- we need standardization and better assays. Again, it's a viral disease. When we can measure it accurately, then some of the other surrogates of immunologic antibody development may be less important than persistent hepatitis B virus suppression.

So, lastly I think we have to be concerned about what we learned about monotherapy, particularly drugs that can develop resistance in treating HIV with nucleosides, but we can also learn from that and move very quickly into trials and experiments and studies that teach us something and move faster and learn from the past. So, immediate moving into combination trials, for example, is clearly the way to go.

So, I also think that the efficacy has been shown in the trials to date. The primary endpoint was histologic improvement. It was clearly met in three studies with very consistent results, and we all have the same questions which we'll spend the next hour or more

trying to discuss.

So, we now move to the vote before we discuss the other questions. The voting members present are just a few actually: Drs. Diaz, Hamilton, El-Sadr, Masur, Hollinger, and me.

I would restate the question for the record. Does the information presented by the applicant support the safety and effectiveness of lamivudine for treatment of chronic hepatitis B? The voting members, if your answer to this question is yes, please raise your hand.

(A show of hands.)

DR. HAMMER: It's unanimous obviously.

So, now we are asked to move on to questions 2 to 6, and I must say that this is the longest and most dense list that we've seen in a while. A lot of these issues have been addressed and many of them are intercalated. So, for the record and the people in the audience, I'm going to read questions 2 through 6. I'm then going to ask the panel members to take some time and really try to address the aspects of these that each one feels comfortable with and try to present some cohesive suggestions to the sponsor and the agency.

The questions that we're now being asked to deal with are the following. What post-marketing information is desirable to determine optimal use in

patients with compensated chronic hepatitis B disease, such as those included in the principal phase III trials, and in other populations such as pediatric patients or patients with decompensated liver disease?

Next, how should the following events influence decisions to stop or continue therapy: e antigen seroconversion, development of viral resistance, reappearance of viral DNA during therapy?

How should patients be monitored for safety and effectiveness during and after therapy?

How can the optimal treatment duration for specific patient groups be defined?

Next, question. Please discuss the implications of viral resistance development for long-term use of lamivudine monotherapy. What recommendations can be made for future development of combination therapy?

Next. To what extent can virologic and serologic results be used as a proxy for histologic changes? Please discuss the relationship between either virologic/serologic or histologic changes and long-term outcomes such as cirrhosis and hepatocellular carcinoma, and how such relationships can be confirmed.

And lastly, what information should be made available to physicians and patients concerning potential effects of lamivudine treatment for hepatitis B on

unrecognized or untreated HIV infection? What are your recommendations regarding ascertainment of HIV status for treatment of hepatitis B with lamivudine to avoid inadvertent use of a single nucleoside analog in an HIV-positive patient?

I think the last one is somewhat rhetorical but the easiest to answer.

I would like to start on my left with our guests and consultants. Dr. Fletcher, would you like to address these in sequence or whatever you feel comfortable answering within the span of a reasonable -- before midnight.

(Laughter.)

DR. FLETCHER: Thank you for clarifying that.

I guess maybe I'll start with number 2 and the optimal dose issue. I think it has arisen in the comments of several individuals whether we have the optimal dose.

As I mentioned in an earlier question, I think the pharmacodynamic modeling for the short term are very convincing about a plateau effect once doses above 100 milligrams are reached. But the pivotal studies went for longer than 6 months out to 1 year, and it's there that we saw the loss of response and emergence of resistance. And I think a natural question has to arise as to whether we really have an optimal dose or not. So, I think data that

I and probably others would like to see is does the use of larger doses affect the proportion of patients that achieve a response, duration of response, and the emergence of resistance.

With regard to the pediatric patients, I think the pharmacokinetic information that are provided in the packet indicate that the proposed dose scales very well in terms of pharmacokinetic equivalence between pediatrics and adults, but I don't believe that we could rely just on pharmacokinetic information, that if you achieve equivalence there, you will then have an equivalent effect. So, longer-term studies of children I think clearly need to be done.

I think maybe the next issue that I would probably want to jump down to is related to question 6, and that is the issue of the co-infected patient with hepatitis B and with HIV. While I think the recommendation in that case to use the 300 milligram daily dose for HIV is very reasonable, it does pose some unknowns in that the safety of the drug for hepatitis B is for a lower dose. The effectiveness was for a lower dose, and is there something disease-related that could affect at least safety when using a higher dose?

But it's also the issue of I guess the addition of lamivudine for treatment of hepatitis B in patients that

are not receiving that drug for the treatment of HIV, and does that additional nucleoside, most likely on top of additional nucleoside therapy, then pose any safety or efficacy concerns? I think the practical recommendations on how to deal with that I think remain a real unknown, at least unknown, not clear in my mind.

I think at least for right now, Scott, I'll stop.

DR. HAMMER: Thank you.

Ms. Melpolder, do you have comments?

MS. MELPOLDER: I think I would use lamivudine judiciously. I wouldn't use it unless there was a reason to use it. I would be concerned about the resistance to the drug and consequently that would be something that I would take in consideration if I were going to use the drug on an HBV positive person.

As far as the HIV, it seems to me that you would have to determine the HIV status so that you wouldn't do harm to the patient by putting them on lamivudine.

I'm not sure what you could use to determine when to stop drug or whether to continue drug. I guess since we know that the e antigen seroconversion seems to be fairly durable and the viral resistance seems to be to me the big stickler, I would go on viral resistance.

DR. HAMMER: Dr. Hollinger? Thank you.

DR. HOLLINGER: It's hard to pick which one to talk about.

Just a couple of things. I think the patient with decompensated liver disease I think is a really critical group, and those of us who have taken care of patients who look like they're really doing very poorly and have treated them with lamivudine and seen a relatively good response in these individuals have been very encouraged with the possibility that this could be a bridge at least to liver transplant for the short term. I think those issues are going to be most helpful, as well as the issue about the use of lamivudine in the transplant arena since it would be considerably less expensive than the use of hepatitis B immune globulin. So, I think that's an area that clearly needs to be evaluated.

The question of number 5 about to what extent can virologic and serologic results be used as a proxy for histologic changes is really an important one. In hepatitis C it was really fairly easy. I think we all, after a while, came down to the fact that we really don't need liver biopsies. I know the FDA always wants to have liver biopsies, and I think we've tried to argue with them many times that, look, you don't need it for this disease. There is plenty of data out there that suggest that looking for normalization of the ALT and a reduction in HCV RNA is

sufficient, that the correlation is excellent.

I'm not sure I've heard that yet with this data, but I'm not sure that I really have the data to look at it. There was some information that the FDA presented which suggested that if they met criteria, they met the seroconversion criteria, that you were very likely to find histologic improvement.

On the other hand, there was a fairly large group of patients that did not meet the seroconversion criteria, and because it wasn't put in there, I don't know if they meant both HBV DNA, the absence by the test that is used, and normalization of the enzymes, or one or the other, or both.

Then there was a fair number of them that had histologic improvement despite the fact they did not meet the seroconversion criteria. But I don't know again if histologic improvement there met fibrosis or a change in necroinflammatory activity. I might look more favorably if it meant fibrosis than I would if it was necroinflammatory activity.

So, that kind of data is probably there. I guess just haven't either seen it or wasn't aware of it. It may have been in the booklet here. I thought I looked through most of that, but I could have actually missed that data.

But I do think that's really critical because it is hard to get patients to agree to another liver biopsy 12 months later, and that is often required or asked by the FDA. I have to be honest. I really disagree with that requirement. Certainly you need a baseline to know where you're starting from, and I would probably feel reasonably good if a patient showed a remission in their disease by an absence of their HBV DNA and a normalization of ALT. This will probably correlate very well with the histologic change. But I would like to see and hope to see perhaps they could provide more information regarding what these changes mean and where there's a better correlation either with the HBV DNA or with the ALT and these histologic changes. So, I think that's something that needs to be looked at more carefully.

DR. HAMMER: Thank you.

Dr. Sjogren.

DR. SJOGREN: I think that the information that I would like to see, after marketing is approved, is that they tell us what are the serious adverse events that continue to be observed in these patients. Obviously, I would like to know what is the duration of the e antigen seroconversion, and by and large, I would like to know everything there is to know with the long-term follow-up of the patients that were treated in the registration trials.

As I said before, decompensated liver disease is a must. We need to make some attempts to look at those patients even if they are not well-controlled.

With fear and trepidation, I must disagree with Dr. Hollinger, one of my mentors and beloved friend.

(Laughter.)

DR. HOLLINGER: Go ahead. Stick it.

(Laughter.)

DR. SJOGREN: And on my knees --

(Laughter.)

DR. HAMMER: You just have to change seats.

DR. SJOGREN: I would say that were it not for liver biopsy in the studies that we have just seen, we would be totally confused. Indeed, it is the histological improvement that was shown by the registration trials which has swayed my mind and maybe some other people's minds because that's really where it's at. We want to see people that have a histological response. Particularly now they will learn that the e antigen seroconversion and the DNA maybe is not all what we hoped it to be.

With one request to the sponsor -- and this is borrowed from the experiences with hepatitis C -- that they don't biopsy at the end of treatment, but that they biopsy at the end of follow-up so we can look at the effect of the drug away from the last day it was given or the patient

might have taken the drug that week and be biopsied and there's always the speculation whether you're still under that kind of influence. So, in hepatitis C we have moved away now. 6 months after stopping the drug or 3 months after stopping the drug, that's when we biopsy and see whether there is an effect or not.

So, I would plead for continuing with liver biopsies. I do them myself. I know how hard it is. I have to convince patients. And it is much easier to do a blood test, but I think in terms of understanding what we're doing, we still need to continue doing that test.

Certainly I am very curious and want to know what happens with the combination of interferon and lamivudine, and I think that's a must, that those studies need to be done again with a sufficient number and a clear design that could answer the questions. Obviously not every patient can go on interferon and lamivudine. They're both powerful drugs and they have to be patients that can tolerate both. But I think for what was presented to us, I could see a ray of hope. I could see light at the end of the tunnel, and I would like to pursue it and know that I can offer that to my patients.

The HIV question. Obviously patients need to be tested before treatment, but then how often? That's a very serious question, especially in risky populations. In

the military, we are tested every year whether we want it or not, so we know our status of HIV or hepatitis. You name it, we know it. We know even our DNA. I'm told we have no constitutional rights.

(Laughter.)

DR. SJOGREN: So, in our population it's a must.

But what about the clinics where that is not a must? Maybe testing every 6 months, every 12 months, I don't know because I don't deal in that world. Certainly when we deal with IND drugs and we face possible pregnancy, we test every month. I don't know in HIV. I think I would have to defer to my colleagues that deal in that arena in alerting us and the public what is best in terms of HIV testing, but it worries me that some people could get monotherapy with the obvious complications of it.

I am disappointed in terms of the lack of histologic changes and serology results. I mean, it's dogma. When I was trained in hepatology, it was dogma to us that they went hand in hand, and I think the importance of these studies, that the textbooks have to be rewritten now. There's no such thing and we have to just face it. It's not the fault of Glaxo or lamivudine. It is just the way it is and we just need to be alert to that.

So, again my plea for liver biopsies in these

patients. Thank you.

DR. HAMMER: Thank you.

Dr. Lee.

DR. LEE: I guess I've already shot my load on a couple of questions before. But I just want to touch on a couple of points.

The patient with decompensated liver disease. I think we all have one or two or a few cases of patients who are on a transplant waiting list and were treated with lamivudine and had a dramatic response. In fact, there is a Canadian abstract that looked at it. I think this is the kind of very encouraging and significant -- these patients often have no other therapeutic recourse at all, and this is a very encouraging development, that some of them improve dramatically to the extent that they come off the transplant list altogether. I've had a patient go from a Child-Pugh C to an A on nucleoside analog treatment. So, I think this is an area that really bears further investigation.

Question 3 about all sorts of questions about when we stop or continue therapy. Well, gee, I wish we had some answers. It would make sense to me that when someone has an e antigen seroconversion with development of anti-e, that that would be a reasonable time to think about stopping.

As for the other questions about resistance or reappearance of DNA during treatment, I don't know. I guess we'll just have to wait a few years for those answers to come out.

I have a little note here just about this decompensated disease. I would like to interject a plea of caution in that I've just recently lost a patient. It wasn't this drug. I've treated with a nucleoside analog a patient with cirrhosis, fairly advanced, just because we had no other options, and he was replicating. Our transplant program won't transplant replicating B patients.

After giving him a nucleoside analog for 6 months, it was e antigen still positive, DNA still positive. I stopped the drug, also at his request because it was costing a fortune. The patient decompensated very dramatically within 2 to 3 weeks of stopping the drug, went into a very progressive liver failure with eventual hepatorenal syndrome and died.

I think this points out that with any new drug or technology, that we really need to be very careful. I would suggest that clinicians don't go about willy-nilly just giving people with decompensated disease these nucleoside analogs, or if they do, that they consider that this is probably going to be indefinite treatment in this special group.

Again, I'd like to echo Dr. Sjogren's comments about the plea for development of combination therapy. I really think that is the future, despite what the data from the 3010B study showed with the active control, not just combinations of interferon and lamivudine. We know that other nucleoside analogs develop mutations at different sites, and perhaps the key to overcoming the YMDD mutant is to give those patients another nucleoside analog that develops a mutation at a different site, analogous to the fashion that HIV is currently treated.

I'm Canadian, so we're expert at sitting on fences and not taking a firm stand. So, I'm going to sit on the fence equidistant between Drs. Hollinger and Sjogren in terms of liver biopsy. I think they're indispensable in clinical studies, especially these registration studies. But in clinical practice, I don't really think they're necessary for the vast majority of patients. Certainly trying to get many of my patients, almost all of whom are Asian, to agree to a first, let alone a second biopsy is virtually impossible, akin to trying to get the American media to stop reporting the Clinton/Lewinsky scandal. It's okay. I'm Canadian, so I guess I'm allowed to say that.

DR. HAMMER: We were going to try to avoid getting that into the transcript.

(Laughter.)

DR. LEE: Unfortunately, this question that you've posed about the relationship between the virologic or serologic data and the histology in the long-term outcome such as cancer and cirrhosis are, unfortunately, because so many drugs are coming about on the scene, not just interferon, but this drug and others due to appear shortly, I don't think long-term studies are going to be possible. This is unfortunate, but it's going to be hard to find a cohort of untreated controls to see the natural history and the effect of these analogs.

Anyway, I think I've said enough.

DR. HAMMER: Thank you.

Dr. So?

DR. SO: I think the previous speakers covered pretty much all of the stuff I'm going to address.

As a transplanter, I also would be interested in having the sponsor have studies addressing whether lamivudine helped to down-stage patients waiting for a liver transplant. We probably all have some anecdotal cases where a patient was listed for emergent transplant and, with lamivudine treatment, they stabilized and was discharged from the hospital without having to undergo emergent transplant.

But on the other hand, I'm also concerned about the emergence of YMDD mutants in patients pre-transplant,

and we should restudy whether that would affect the recurrence rate after transplantation.

Also, as a person who also performs liver resections, it's well known that after liver resection in patients with chronic hepatitis B, the 3-year recurrence rate even for small tumors is as high as 70 to 100 percent. So, it will be interesting to see whether treatment of these patients after liver resection can help to reduce the recurrence rate.

Also, as a children's advocate, I think it's very important to study the long-term treatment effect in the pediatric population.

As far as the treatment endpoint, it would be simple to adopt HBe antigen seroconversion as a treatment endpoint, but once again, I'm not sure whether that really is adequate, and I would hope there would be long-term studies to address whether long-term lamivudine use, as long as the patient has suppressed HBV DNA and normalization or near normalization of ALT, helps to decrease the long-term sequelae of the infection.

Lastly I want to just make a few comments about what I'd like to see in terms of combination therapy. Definitely we should think about combination lamivudine therapy with other nucleosides or nucleotide analogs to see whether that would decrease the incidence of recurrence of

mutant development.

Also, since lamivudine only suppressed the viral DNA and doesn't get into the hepatocytes which in fact live inside the infected liver cells, once again I'd like to echo my previous colleagues that we should, once again, do a good study with lamivudine with interferon or other newer modes of therapy which cause apoptosis of these HBV infected hepatocytes.

Thank you.

DR. HAMMER: Thank you very much.

Dr. Stanley.

DR. STANLEY: I'll go to number 6 first.

As far as testing to recognize HIV infection, my knee-jerk reaction is to say that it would be required because it's unfortunately still all too common for people to stereotypify the risks for HIV and to underestimate their own or their patients' risks for HIV. So, I would tend to be more bold and say that testing should be required, but there may be modifications we can make on that.

The other thing, in regards to the co-infected patient, is not only should the clinician be instructed to use the higher dose, but should be aware that in the patient who is not requiring treatment for his HIV yet, a commitment to use lamivudine for his hepatitis B really

probably commits that patient to the full triple drug therapy for HIV which is the standard now, so that it's a more complex decision. I don't know how many hepatologists would be educated enough in that since many infectious disease and internal medicine docs aren't educated enough in that yet. So, that would be an area where consultation might be required.

With regard to question 2, again I think we need a commitment from the sponsor for some long-term follow-up of these patients to see what the outcome is. I hate to take the analogy and the experience too far, but I don't want to see 3-year Concord follow-up come out here and we find out that our monotherapy has not done a good job. So, I think we need a commitment there.

Certainly still I have questions about the dose appropriateness.

I think that we need a sponsor, to echo other comments, for looking at combination therapies with not just interferon but other nucleosides.

Finally, with regard to question 3, I agree that e antigen seroconversion is probably a good time to start thinking about stopping therapy. If we can learn anything, though, from our HIV experience, reappearance of viral DNA or viral RNA in the case of HIV on triple therapy has been used as a trigger point to consider changing

therapy, but yet anecdotally people are still seeing good clinical responses despite what we call a virologic relapse. So, I'm not sure that reappearance of viral DNA in hepatitis would be a reason to stop therapy. I don't know if we can compare those two experiences, but I just throw that out as a thought.

I think that's all I'll say.

DR. HAMMER: Thank you.

Dr. Yogev.

DR. YOGEV: Well, first, I think the major problem we didn't address is what happens to the patients after you stop therapy. I was quite impressed with the number of patients who had liver enzyme elevation when you stopped it. There are already two reports in the literature about liver failure following lamivudine, and we also have to be very careful because there's one case reported, at least that I'm aware of, of a combination of lamivudine and stavudine that on therapy caused liver failure. So, I think this issue of the effect post-therapy has to be followed very closely.

I would like to see the drug really being limited to the most severe cases because of the shortness of disease, before transplant, for example. It's an excellent example.

I hope that the agency somehow will hold the

company unlimited time for adult to make sure that the pediatric, the pregnant women will be also part of the studies so we know what to do with them. As far as I'm concerned, 6 months of positive antigen is chronic disease. Every newborn who got the infection for 6 months is chronic of this disease and we need to work it out.

We didn't talk at all about compliance. I think that's a major issue. Being an HIV person, for many years I believe it's a virus and I think the reason why I believe in that is because we did not yet affect the immune system enough with reduction of the virus, and what we're seeing over here is probably a limited effect on the virus which we don't see because of diagnostic tests which we need to develop. That's why the immune system which we try to follow is not as good.

Therefore, to avoid liver biopsies, I think we need to look into the virus itself, and when we see it's coming up, that should be a point to the physician to start investigating compliance versus efficacy of the drug. According to the liver status at that time, I would stop and start because I don't think there is a major problem stopping because we were told amply that the wild virus is coming back. So, we can correlate now what happened to the liver at that point in time and then stop. So, we have some parameters how to decide the more aggressive disease

to approach and when to stop and start with the limited weapons we have.

As for the HIV testing, I think if we start treating because it's 1-point mutation for HIV and that's it, that maybe some recommendation to discussion with the patient that as we test the liver enzyme or whatever once a month or whatever, we should then test for the HIV to catch if the unfortunate patient got the HIV infection, that we catch it early enough to not have a longer period of time on monotherapy and we know what happens.

As for combination therapy, I think we have to insist on doing it because I think the handwriting is on the wall. All of us are seeing it. Just because we are desperate, I think this drug should be approved but, as I said, to a limited population.

DR. HAMMER: Thank you.

Dr. Hamilton?

DR. HAMILTON: I would like to see the committee lay the mantel of responsibility directly at the feet of the sponsor to perform all of the following concrete ideas, my ideas.

(Laughter.)

DR. HAMILTON: First of all, I think it's very important that the sponsor emphasize the proper patient for whom this drug is indicated. To extrapolate beyond the

experimental evidence would seem to me to be a shame and asking for trouble in all kinds of ways, many of which you wouldn't want.

Secondly, I think the sponsor should assist in the development of a more sensitive test for this virus, one which would give us substantially greater confidence that we are doing something beyond simply suppressing.

Third, I think the sponsor is in a position, an ideal position I think, to provide us with ongoing evidence of the rate at which emerging resistant viral strains are occurring. The trials are in one sense over, in another sense not, and I believe some extremely valuable information can be obtained there. And I believe the sponsor could assist in the establishment of standards, arbitrary as they may be at this moment based on incomplete information, to define failure of therapy. I don't think we can divine what that is at this moment. We need to find out and test the hypotheses.

To that end, I think you could set up a clinical registry, including all of the patients that you've enrolled to date, and test hypotheses that are generated in the course of the various deliberations that have gone on here today and in your own offices.

There are some subsets of patients who I think should be studied in substantially greater detail. I've

already mentioned that I thought the pregnant woman and her newborn are critical. It certainly has proven to be the case with HIV.

I'll echo the recommendation that combination therapy using non-nucleoside, other classes of drugs will inevitably become essential. What those are I wouldn't know at this point, but it should be explored.

Lastly, I'd like to make an appeal for this drug to be more affordable to the individuals who will ultimately use it. I don't know the impact which this committee has on those kinds of decisions, but I can tell you that it's a very, very real element in both the decision to treat, to extend therapy, and we're talking here about treatments that may be lifelong. Who knows.

Those are my recommendations.

DR. HAMMER: Thank you.

Dr. Diaz?

DR. DIAZ: Thank you.

I'd like to just address a couple of the questions, in particular question number 2 about post-marketing information. I'm still struggling with trying to answer the question when would it be best to start therapy in addition to questions about when would one stop therapy. I certainly agree it's a drug not to be lightly taken and certainly not for all patients. Yet, there is this

interesting data in the Asian population that we've struggled with today a little bit about is there something unusual about that population perhaps that lend it to better outcome in terms of at least less resistance and sustainability. One of the important criteria that was alluded to was that in this particular study, likewise the Asian population was perhaps less progressed in their disease at the time of entry.

So, it does bring up some interesting questions about when might one want to start therapy, and in particular I think we need some predictors of a response to therapy. If we could in some way be able to better identify patients who would respond to therapy before we even start, we might have a better ability to choose the patients that should be treated with this drug.

I think the dosage of the drug has been dealt with by multiple individuals and I won't go into that any further.

Certainly how long to treat or perhaps when and how to retreat an individual is an extremely important question to answer.

Likewise, should one continue to treat despite perhaps the reemergence of detectable HBV levels?

As far as the decision when to stop therapy, I have even more difficulty grappling with that question. In

terms of e antigen seroconversion, in order to sort of answer that question in my mind, I think it's important to know what the durability is off therapy, and I'm not sure we have the answer to that particular question. So, although e antigen seroconversion is perhaps a good marker for considering stopping therapy, I think we need more information to know what the durability is off therapy in order to use that as a decision point.

Likewise, in terms of developing viral resistance, it's another issue to deal with that I would not want to address at this point, but more so tackle the issue about reappearance of viral DNA. Many individuals in the study did have reappearance of viral DNA. And yet I think it's important for some criteria to be set as to how many times one might be tested, over what period of time in order to assure that viral DNA has reemerged, and if so, is that a criterion for stoppage of therapy? I'm not sure. It seems in some of the data that was presented in those individuals who had reemergence of viral DNA, only about half of those patients had YMDD mutants detected. So, again I think we need more information about long-term reemergence of viral DNA perhaps and over what period of time before we use that as a solid criteria for stoppage of therapy.

The last couple of comments that I think I

would make would be to address the fifth and sixth question, the fifth question in particular, to what extent can virologic and serologic results be used as a proxy for histologic changes? I think it's an important question to try and answer because we've heard different opinions today about the use of liver biopsies or at least the willingness to do liver biopsies. I think we need to continue the recommendations to follow liver biopsies because I don't think we'll answer a lot of the questions without having that and organ response to compare to.

And in particular for virologic, I was looking at the FDA's table that they put together, table 7, in trying to sort out that question as far as virologic response to be used as a proxy for histologic change. It seemed to me that with those individuals who were persistently suppressed, there was a fairly decent correlation or at least a higher percentage of histologic responders, but if there was reemergence of viral DNA in particular, there was some decrease in histologic response. And perhaps further elucidating those individuals, coupling their reemergence with perhaps the development of mutants, that type of data might further sort out those individuals in terms of the reliability of virologic response as a marker for the histologic response.

For those individuals who had late suppression,

though, I'm not sure if we followed them out far enough to really be able to tell if one could then go on to use their data to support the histologic response pattern. Certainly in those individuals who were unsuppressed, they seemed in my mind not to be much different in terms of their scores than those individuals on placebo.

So, I think there's perhaps some validity in looking at virologic response and coupling it with histologic response, but I think we need to continue to monitor and do further studies looking and correlating it with liver biopsies. And if we stop doing that, we won't get the answer to those questions.

Finally, in special patients in particular, I would very much want to see data in pregnant women in particular because 5 percent or so of perinatally acquired HBV occurs in newborns who are born to HB surface antigen positive moms where the baby has received HBIg and vaccine appropriately at birth. So, there's a small percentage of babies who, despite the use of good preventive intervention, will go on to be chronic carriers. So, I very much would like to see information coming out in the future on pregnant women.

As far as the pediatric population in particular, I think the question when to use this in the pediatric population is an extremely important question to

answer, how long to treat pediatric patients. I don't think we have the answer to any of these questions obviously. And when might we use it and get the best long-term effect without sort of playing all our cards at too early a time in these young individuals' lives?

More importantly, how could we best avoid mutations and perhaps what might the effect of puberty on the disease progression and likewise interactions with treatment?

There are other individuals, special groups, that could be mentioned such as transplant patients. In particular, I think we might be able to get data on hepatocellular carcinoma development, get that question answered more quickly in those patients than in other patients.

Also, I would like to see some information on patients who are on immunosuppressants like prednisone and other immunosuppressants and their effect on therapy.

I should stop.

DR. HAMMER: Thank you.

Dr. El-Sadr.

DR. EL-SADR: I do think that this drug provides a wonderful opportunity for the sponsor, in conjunction with others, to really try to answer some very key questions about this virus and its treatment. Probably

it's going to require continuing to do more and more studies because we've learned a whole lot from this study, but I think it's opened a whole lot of other questions that are key to managing chronic hepatitis B infection.

I guess in my own thinking, it's hard for me to imagine stopping treatment for this infection with the available agent, with this antiviral, because even when we use the term e antigen seroconversion, it's really a misnomer. It's not seroconversion. We do know that there's a lot of virus there. It's just that our assays are not really very good. So, even at best with seroconversion, there is evidence there's a whole lot of virus in these patients and probably it's going to be unlikely that we're going to be able to cure the infection with the available agent, at least in a substantial number of the patients.

I think, on the other hand, the opportunity to study interferon alfa and lamivudine is a wonderful opportunity with an immune modulator and an antiviral drug. With a nicely design study, we probably could learn an awful lot and maximize the response to this combination treatment. I do believe that it's a combination treatment that's going to ultimately make a difference in the outcome for these patients.

The issue of histology versus serology. Again,

with the state of the art of the situation with the serologic tests, I think we have no choice but to continue to seek better serologic tests that are always in conjunction with the histology. So, I think we're really compelled to continue to use the liver biopsies to look at what happens in the individual patients.

I'm concerned about the issue of the mutants. Although it's reassuring that the wild-type virus does come back after stopping treatment with lamivudine, it's unclear whether retreatment with this drug will be as effective as the initial treatment with lamivudine. So, that also may need to be looked at as well.

Finally, the issue of the HIV infected, I think both HBV and HIV are sexually transmitted as well as transmitted parenterally. So, clearly the population at risk for one is at risk for the other, and it would be wise to strongly recommend HIV counseling and testing for patients who do have hepatitis B infection in general, but even more importantly for people who are going to go on monotherapy with lamivudine.

I think there are some populations where I think this drug offers great opportunity like the transplant patients to prevent infection of the transplanted liver, and a few of the other populations that have been mentioned so far.

DR. HAMMER: Dr. Masur.

DR. MASUR: Most of the major points about the opportunities and problems have been made. A number of references have been made to the fact that in 1998, we're very much like we were in 1987 with HIV. One of the things I think we learned then is that as technology changes, it's very difficult to develop long-term strategy protocols because the technology changes, the drugs change.

Some of the most useful data we got at that point was by establishing cohorts of patients that were followed long term by saving specimens of serum and tissue so that we could go back and relook at those populations based on more sensitive assays, on different parameters that we wanted to look at. So, I guess the only thing I could add is I would hope that these cohorts are maintained in a stable situation so they can be followed long term, the specimens are kept so that assays that are more sensitive or more specific or look at different parameters can be reassessed in light of the natural history. I would think that we would gain a lot of information that way.

DR. HAMMER: Thank you.

Just a few final thoughts. First, on behalf of the committee, I'd like to thank the sponsor for a briefing packet that was well put together and cohesive and for a very cogent presentation today and responsiveness to the

questions.

I just have a few comments. Really I agree with everything that has been said. As far as, just taking some of these points in order, the post-marketing information that's desirable in phase IV is clearly what the long-term follow-up and durability is and the longer-term safety. The question is how to get that. One can do follow-ups from the trials, both controlled and uncontrolled, and I would encourage that.

I think one of the pitfalls in these follow-ups is that they tend to only follow the responders after a treatment course is over or the study is closed. I would suggest that we try to develop a way to look at responders and nonresponders in the long term.

I would echo what Dr. Hamilton said about a registry, and I think this is perhaps one of many instances in which the agency can perhaps bring a number of sponsors together who are developing agents for this disease to try to enroll any patient in a study in a registry and in fact talk about how that registry should be enlarged, particularly at transplant centers that are seeing a lot of patients and already have a transplant registry. The only way really to ultimately find out what we're doing with the longer-term outcomes of cirrhosis, cancer, transplant, and death is going to be that way because no single study or

single sponsor I think will be able to answer that kind of question.

As far as the special populations, they've been well outlined. I would only one thing in relation to decompensated liver disease. One of the new opportunities we have, because the number of drugs are being developed of the nucleoside and nucleotide class is in fact, once quick early phase I/II studies are done with another new agent, to determine the relative safety in a difficult situation as has been done with lamivudine already. One can even then begin to think about controlled trials in that circumstance which to date have not been possible both ethically and also because interferon is not tolerable in that situation. But we will be able, in fact, to do controlled trials in decompensated liver disease when we have a number of agents that at least look relatively safe early on.

As far as the issue of when to stop and when to start, it's very difficult. I think some of the entry criteria for the studies that were done here in phase III, the higher risk patients clearly are the patients to treat, and I don't think we can go too much beyond that at the moment except for some of the compassionate sorts of uses and pre-transplant uses that have been mentioned.

As far as when to stop, I think that's also